

AA4500: Collagenase Clostridium Histolyticum

**Arthritis Advisory Committee
September 16, 2009**

Agenda

Introduction

Benjamin Del Tito, Ph.D.
*Senior Vice President,
Quality and Regulatory Affairs
Auxilium Pharmaceuticals, Inc.*

Dupuytren's Disease and Current Management

F. Thomas D. Kaplan, MD
*Indiana Hand Center
Clinical Associate Professor of
Orthopedic Surgery
Indiana University School of Medicine*

AA4500 Clinical Efficacy

Anthony DelConte, MD
*Chief Medical Officer
Auxilium Pharmaceuticals, Inc.*

AA4500 Clinical Safety Risk Mgmt Activities

James Tursi, MD
*Vice President, Clinical Affairs
Auxilium Pharmaceuticals, Inc.*

Overall Summary

Anthony DelConte, MD

AA4500 (collagenase clostridium histolyticum)

For Injection

- **Indication: Treatment of advanced Dupuytren's Disease defined as...**
 - A progressive disease resulting in fixed flexion deformity (contracture) in one or several joints
- **Dupuytren's cord**
 - Abnormal collagen deposition resulting in contracture
- **Current treatment surgery**



AA4500 (collagenase clostridium histolyticum) *For Injection*

- **Alternative to surgery, novel option**
- **New Molecular Entity (NME)**
- **First in class biological**

AA4500: Two Collagenases in a Fixed Ratio

- Naturally produced by the bacterium *Clostridium histolyticum*
 - AUX-I
 - AUX-II
- Collagenases act in complementary manner

AA4500 (collagenase clostridium histolyticum)

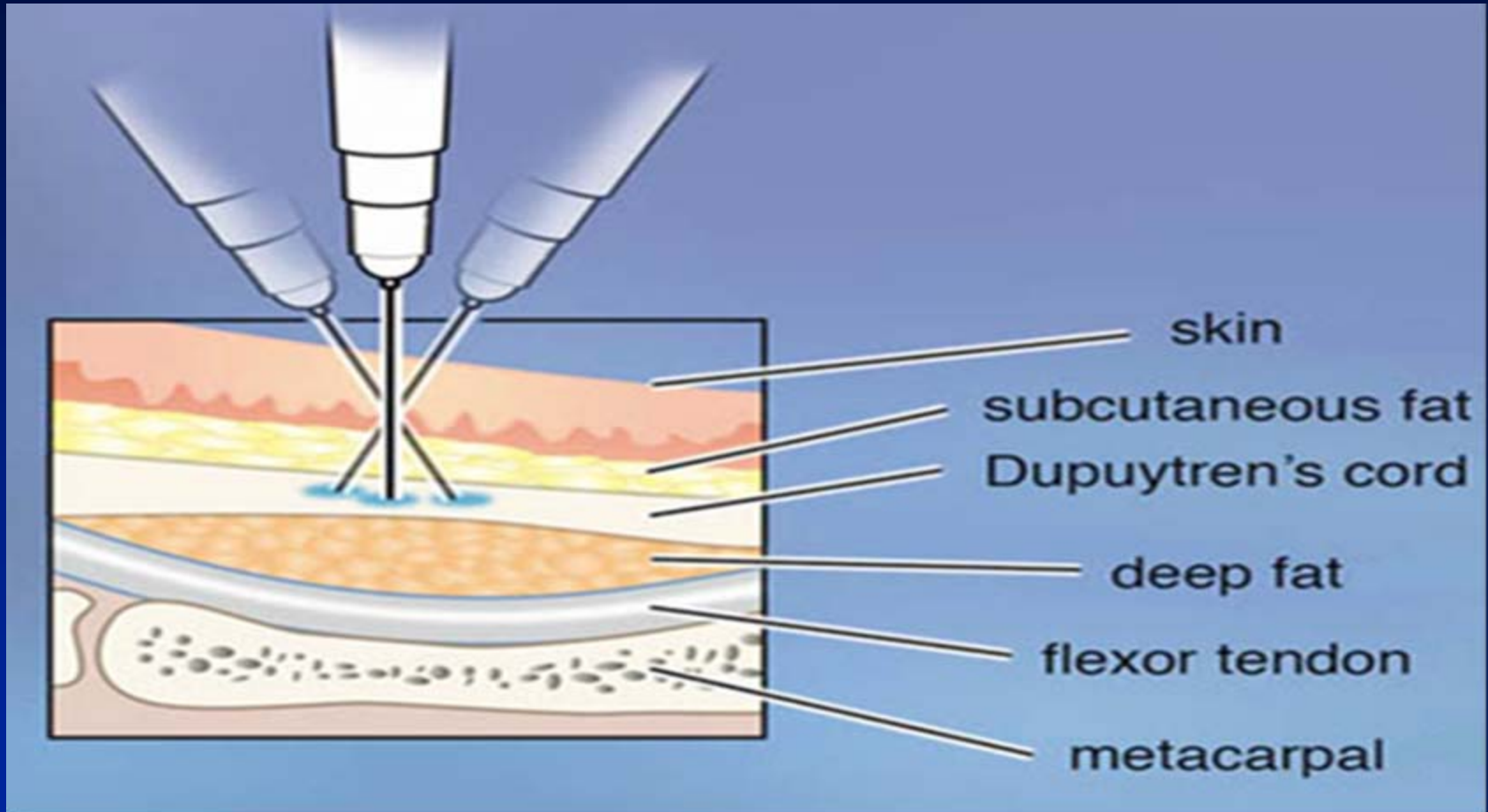
- Dosage form:
 - Sterile lyophilized powder
 - Single use vials
 - Reconstitution in recommended sterile diluent (CaCl_2 and NaCl)



AA4500 (collagenase clostridium histolyticum)

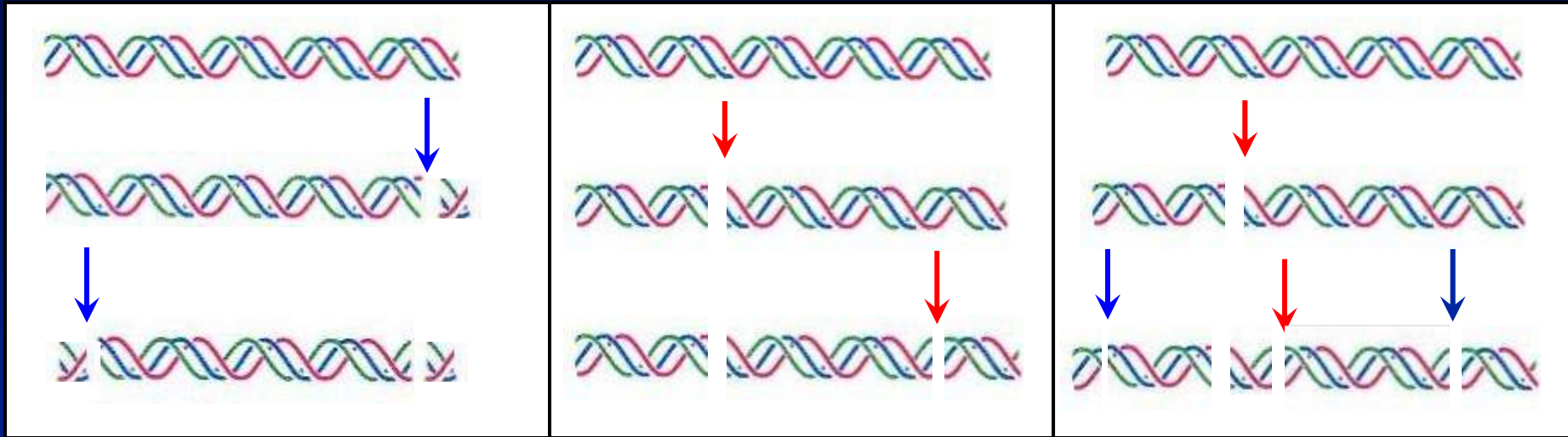
- **Dosing regimen:**
 - A dose of 0.58 mg from a single use vial
 - Injected into the cord (intralesionally)
 - Finger extension after 24 hours to disrupt cord
 - Each cord can receive one injection at 4-week intervals up to a maximum of 3 injections

AA4500 Is Administered by Direct Injection Into Dupuytren's Cords



Once injected, AA4500 acts locally against the collagen components of the Dupuytren's cord

Complementary Activity of AA4500 Components



- **AUX-I (Class I):**
 - Intact collagen
 - Cleaves ends of collagen
- **AUX-II (Class II):**
 - Collagen peptides
 - Cleaves interior of collagen
- **AA4500:**
 - More complete degradation
 - Cleaves multiple sites on collagen

Regulatory Timeline

- **IND #5780 filed on October 5, 1994**
- **Agreement on dose selected (0.58 mg) at End-of-Phase II meeting on August 22, 2001**
- **Auxilium licensed product on June 3, 2004 with subsequent IND transfer**
- **BLA #125338 filed February 27, 2009**
 - **Accepted with Priority designation on April 28, 2009**

Outside Expert Panel Participants

- **F. Thomas D. Kaplan, MD**
*Indiana Hand Center
Clinical Associate Professor of Orthopedic Surgery
Indiana University School of Medicine*
- **Philip A. Waller, MD**
*Rheumatologist
Memorial Hermann Hospital, Houston, TX*
- **Paul Chamberlain, BSc (Hons)**
*Advisory Board Member (Immunologist)
Nordic Drug Application (NDA) Regulatory Sciences
Ltd. (UK)*

Additional Auxilium Panel Participants

- **Theodore Smith, Ph.D.**
Vice President, Biometrics
- **Susan Emeigh Hart, V.M.D., Ph.D.**
Senior Director, Drug Safety and Metabolism

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AA4500 Clinical Investigator

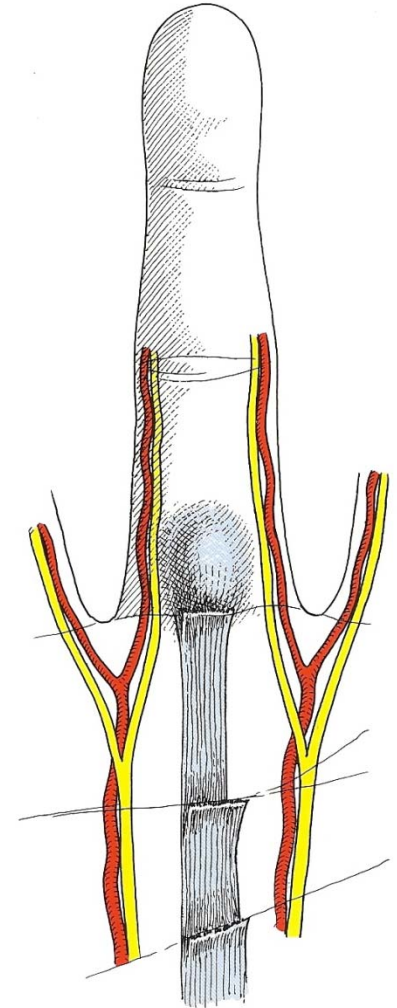
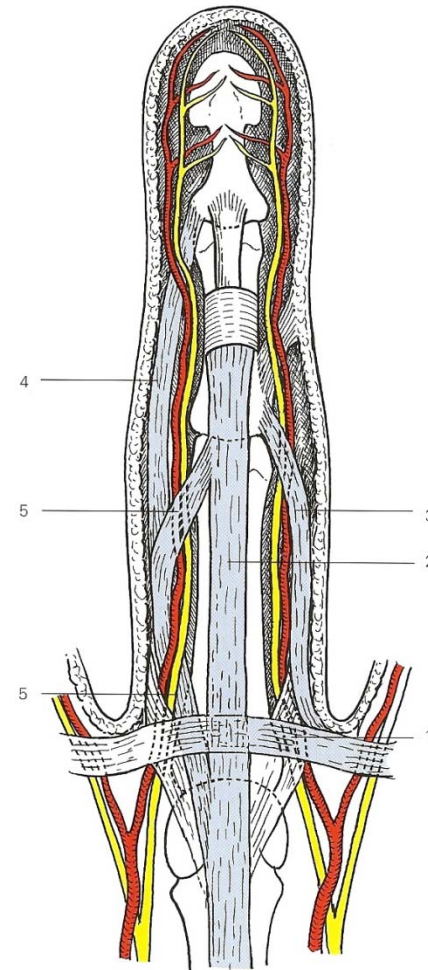
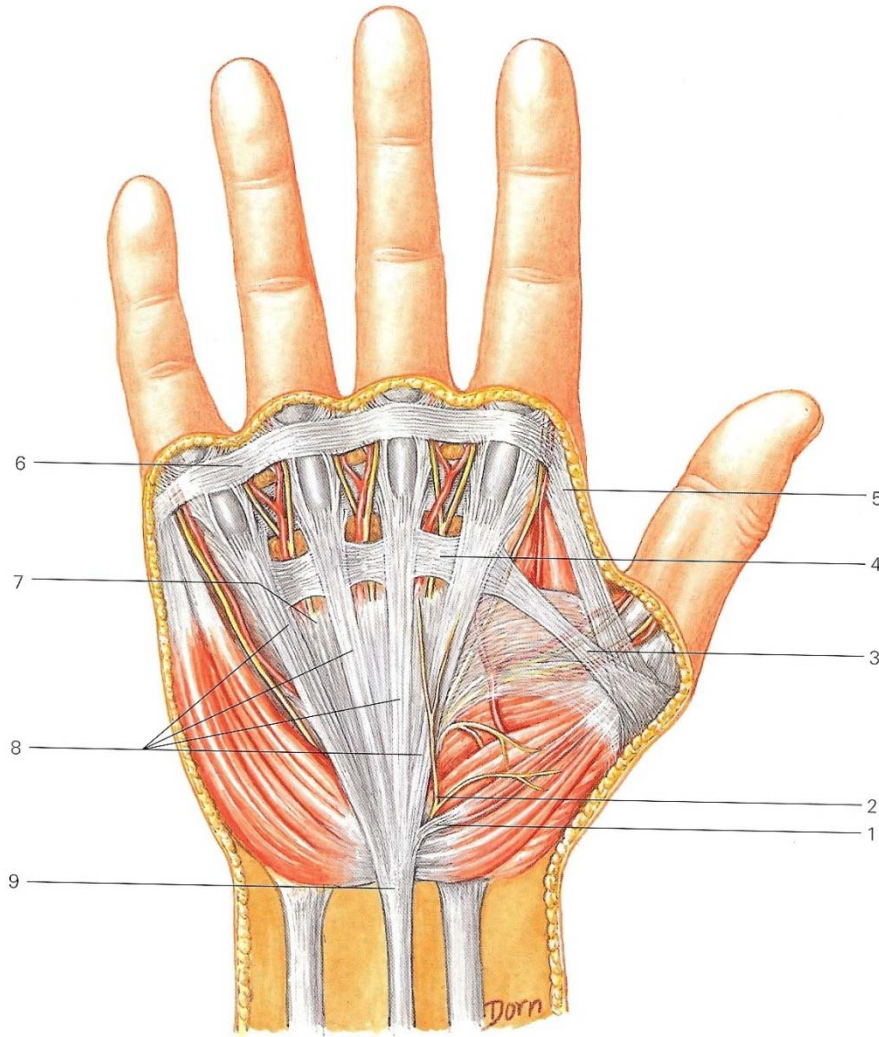
Indiana Hand Center

Dupuytren's Disease

- Abnormal deposition of collagen (nodules & cords)
- Nodules & cords cause joint contracture
- Ring and small finger most commonly affected
- Bilateral in ~ 50%
- Progressive



Pathoanatomy

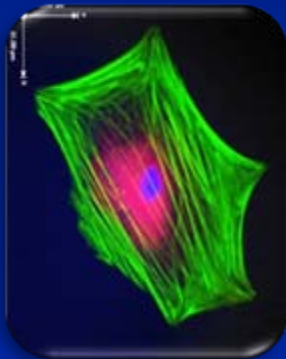


Clinical Stages of Dupuytren's

Early

Proliferative Phase

- Fibroblasts → Myofibroblast
- Nodule formation



Intermediate

Involutional Phase

- Myofibroblasts align along lines of tension
- Nodule thickening and cord formation
- Joint contractures begin



Advanced Disease

Residual Phase

- Continued collagen deposition
- Progressive contractures
- Cord relatively acellular



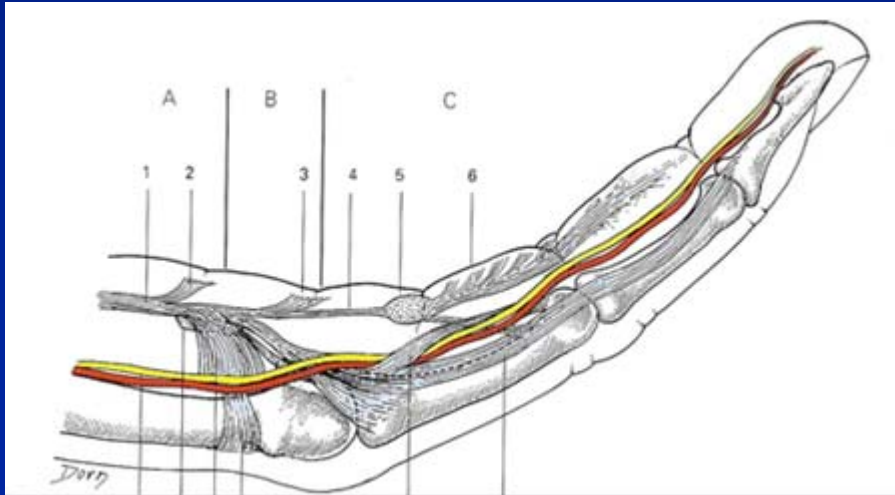
Clinical Presentation

- **Nodules**
 - Follow skin changes
 - Most commonly in palm over MP joint, may form in digits
 - Usually painless
 - May irritate flexor tendons and cause painful tenosynovitis
 - Progress to development of cords



Clinical Presentation

- Cords
 - Firm rope-like structure, usually starts in palm and extends into digits
 - Skin may be adherent to cord and appear to retract with cord



Clinical Presentation

- Joint Contractures
 - Palmar cords cause MP joint contractures
 - Digital cords cause IP joint contractures
 - Ring finger most commonly affected
 - Ring > small >> middle > thumb >> index
 - Contractures may be static or progress to severe deformity



Epidemiology

- **Prevalence of this disease varies in local populations**
- **Familial history**
- **Males >> females**
- **Disease of adult life**
- **Highest incidence in people of European ancestry**
- **More common in Caucasian population**

Etiology

- **Not completely understood**
- **Many associations with Dupuytren's disease:**
 - **Genetic Factors**
 - **Autosomal dominant with variable penetrance**
 - **Familial clustering**
 - **Tissue ischemia (smoking, diabetes mellitus)**
 - **Trauma (Manual Labor)**
 - **Epilepsy**
 - **Alcoholism**

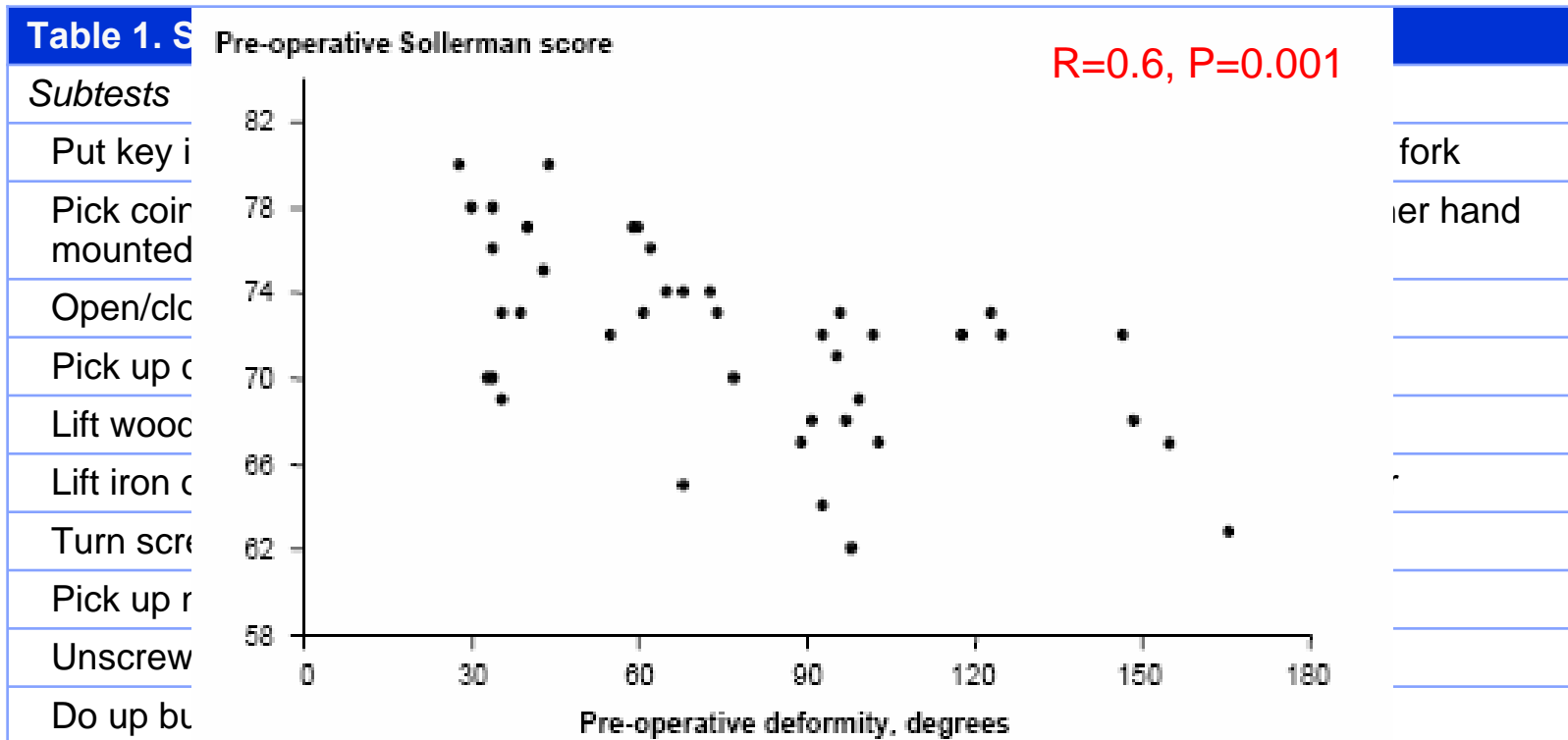
Contractures Compromise Hand Function

- What the literature tells us

FUNCTIONAL BENEFIT OF DUPUYTREN'S SURGERY

R. SINHA, T. R. CRESSWELL, R. MASON and I. CHAKRABARTI

Journal of Hand Surgery (British and European Volume, 2002) 27B: 4: 378-381



Contractures Compromise Hand Function

- What patients tell us
- Decreased function translates into difficulties with:
 - Daily activities (e.g. face washing, combing hair, shaking hands)
 - Job function (e.g. wearing gloves, keyboarding, grasping tools, getting hand into tight spaces)
 - Hobbies (e.g. sports, musical instruments, woodworking)



Treatment Options

- Observation & reassurance
 - Massage and stretching
 - Indicated until functional limitation
- Surgical treatment when:
 - MP joint contracture $> 30^\circ$
 - PIP joint $> 20^\circ$
 - Compromised function
 - Well defined cord
- Surgery not curative
- No effective nonsurgical options

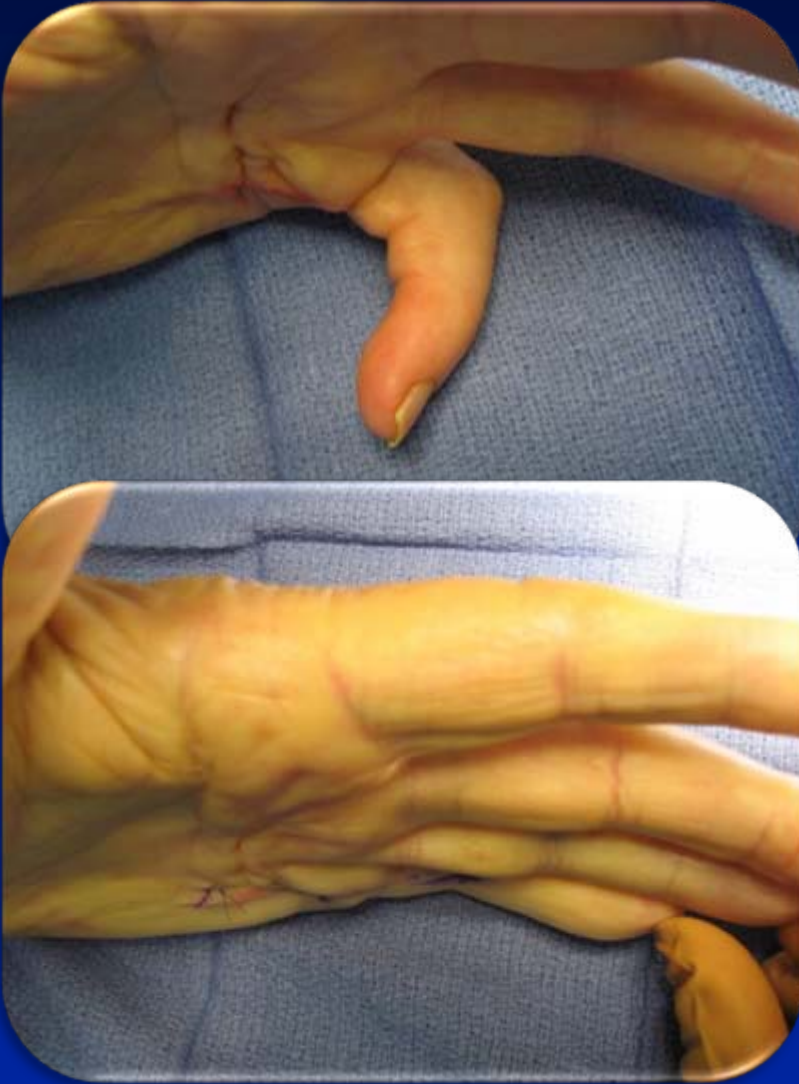


Surgical Management

- **Fasciotomy**
(open or percutaneous)
 - Disruption of cord
- **Fasciectomy**
 - Removal of diseased fascia
- **Dermofasciectomy**
 - Excision of cord and skin
 - Wound covered with skin graft



Fasciotomy – Open



Percutaneous Fasciotomy

PERCUTANEOUS FASCIOTOMY FOR DUPUYTREN'S CONTRACTURE

A 10-year review

R. A. DUTHIE and R. B. CHESNEY

Journal of Hand Surgery (British and European Volume, 1997) 22B: 4: 521-522

- **Results**

	Pre-op Contracture (PIP + MP)	Initial Post-op Contracture	Contracture at 10 year f/u
Average (n=82)	71	22	
No further surg (n=28)	74	21	57
Secondary fasciectomy (n=54)	69	23	85 (at time of 2 nd surgery – mean 5 yrs)

Percutaneous Fasciotomy

Needle Aponeurotomy



Percutaneous Needle Fasciotomy

- **Results**

Author	Badois (1993)	Foucher (2001)	Van Rijssen (2006)
Patients	123 hands	100 rays	55 rays
Recurrence	50% (5 yrs)	58% (3.2yrs)	65% (33 months)

- **Complications ***

- Nerve injury (0.05% - 2%)
- Skin fissure (15 - 50%)
- Flexor tendon rupture (0.05%)
- Arterial injury
- Infection (2%)

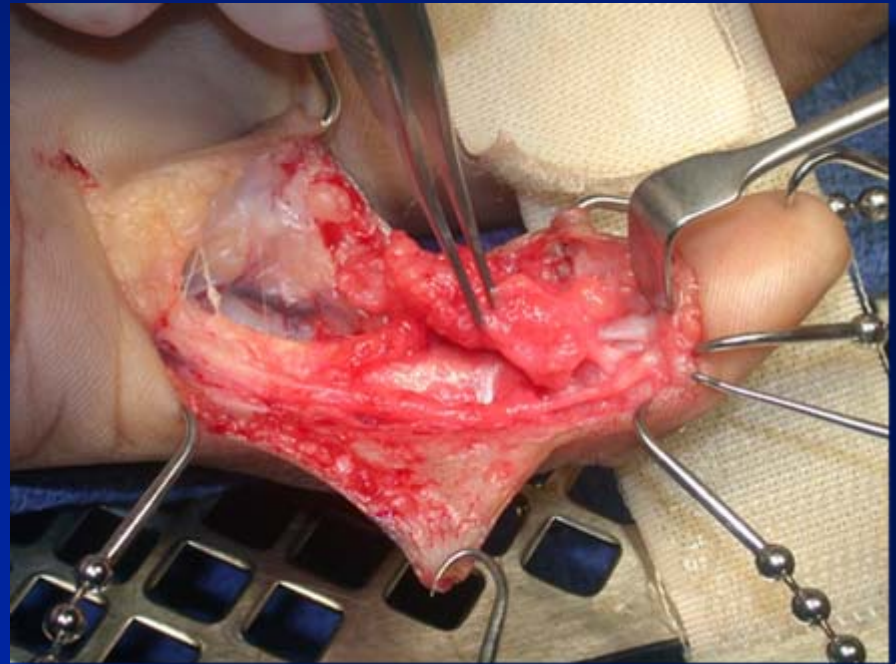
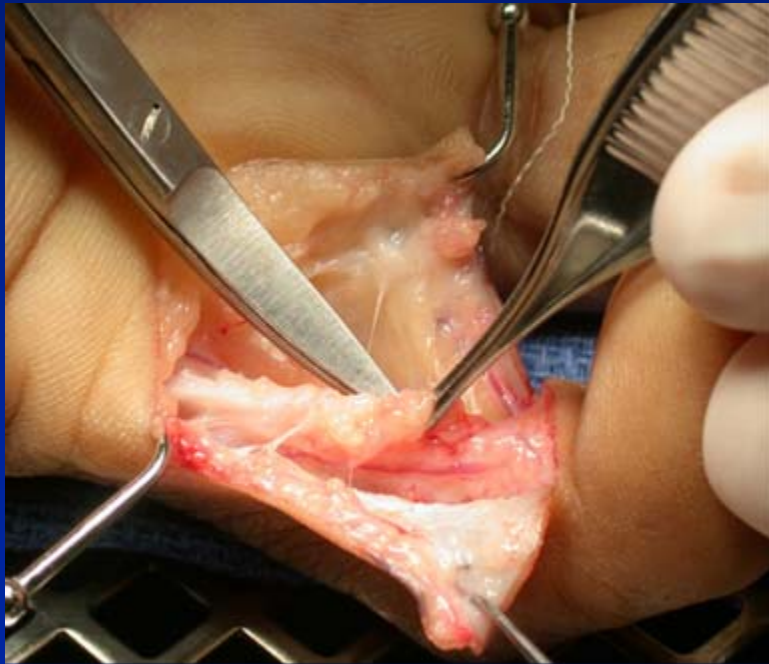
Subtotal Palmar Fasciectomy

- Current gold standard
- Indications
 - MP $> 30^\circ$
 - PIP $> 20^\circ$



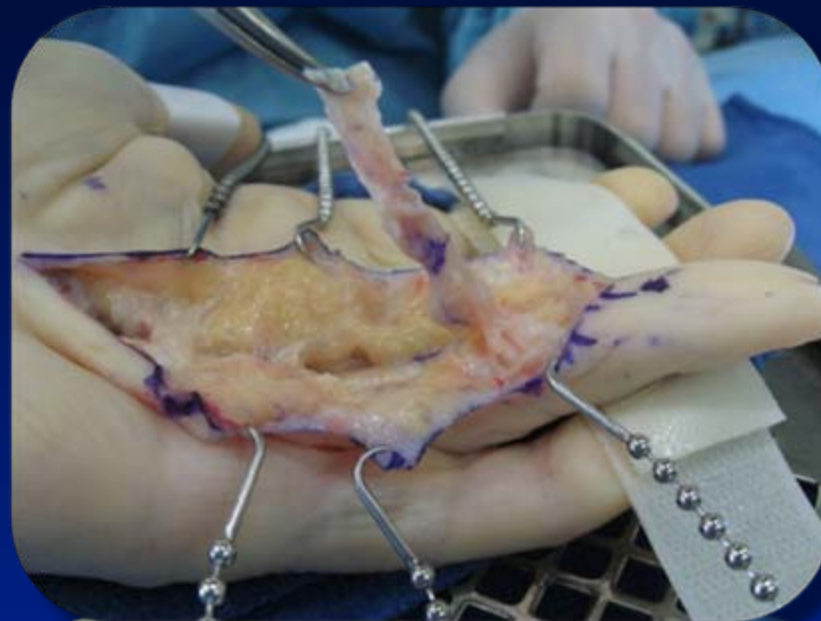
Subtotal Palmar Fasciectomy

- Regional anesthesia
- Extensile approach
- Careful dissection of nerves and arteries



Subtotal Palmar Fasciectomy

- **Excision of diseased fascia**
- **Assess extension gained**
 - Additional cords?
 - PIP joint release?



Subtotal Palmar Fasciectomy

- Therapy begun
POD # 2-5
 - Therapist 2-3x/wk
 - 4-6 x/day at home
- Wound care & edema control
- Range of motion
- Full-time extension splinting b/t exercises (~ 4 wks)
- Night splint 4-6 months

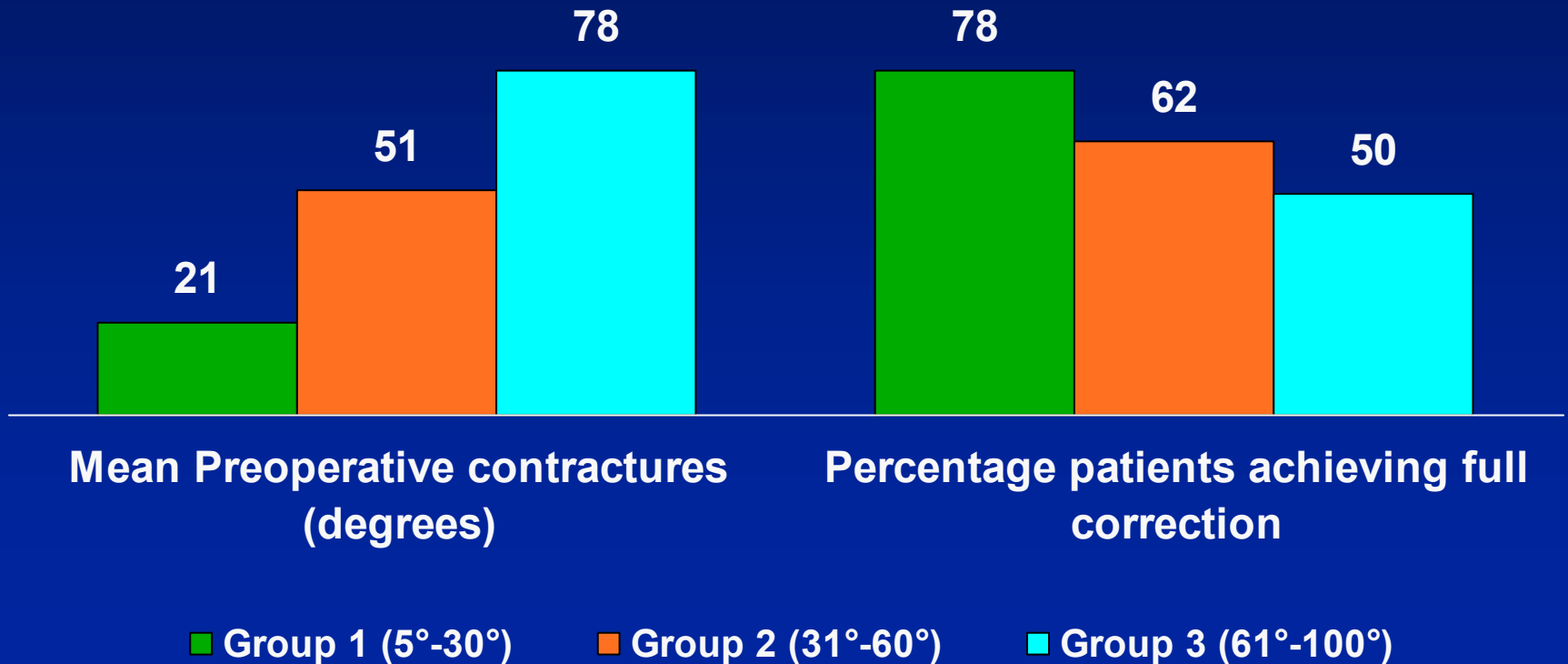


Fasciectomy Results

Results of Surgical Treatment of Dupuytren's Disease in Women: A Review of 109 Consecutive Patients

M. U. Anwar, MBBS, S. K. Al Ghazal, MD, R. S. Boome, MBBS

J Hand Surg 2007;32A:



Fasciectomy Results

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J Hand Surg 2007;32A:

- **Complications**

- Recurrence (f/u avg 12 months)
 - 22% women / 19% men
- Flare reaction – 2%
- Digital nerve / artery injury – 3%
- Infection – 2%
- Loss of flexion / extension



Limitations of Surgical Treatment

- Incision & dissection lead to soft tissue trauma and scarring
 - Post-operative pain
 - Requires 6 weeks to 4-6 months to recover
- Post surgical hand therapy is required
- Complications
- Recurrence
- It's surgery
 - Some patients won't or can't have an operation



Goals of Treatment for Dupuytren's Disease

- Eliminate contracture
- Maintain a supple finger
- Limit morbidity
 - Low complications
 - Minimize pain
- Quick functional recovery
- Low recurrence

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AA4500: Clinical Program Design and Efficacy

Anthony DelConte, MD

Chief Medical Officer

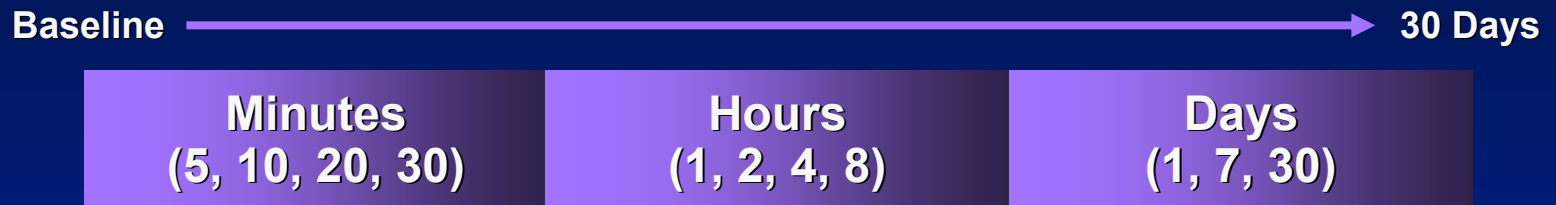
Auxilium Pharmaceuticals, Inc.

AA4500 Clinical Program – 13 Studies

- **1082 Subjects received at least 1 injection**
- **Phase I**
 - **PK study**
- **Phase II**
 - **Proof of concept and dose ranging**
- **Phase III**
 - **3 Double-blind placebo-controlled (N=407) followed by open-label extension**
 - **4 Open-label / other supportive studies**

AA4500 Pharmacokinetic Study Results

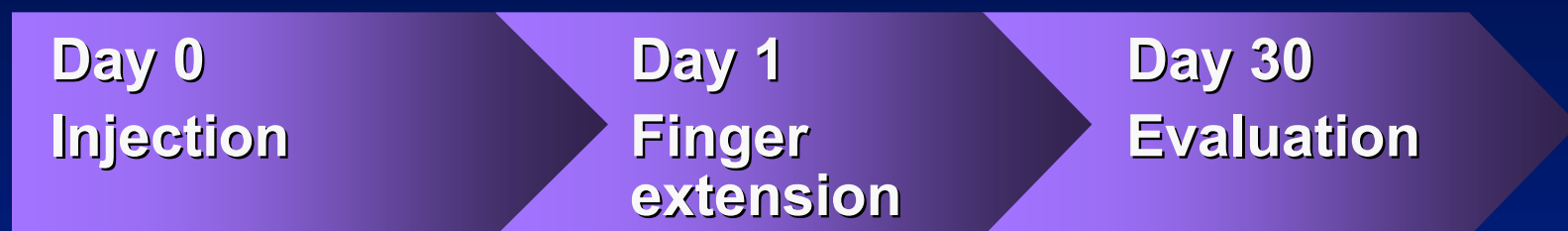
- (N=16)
 - Sampling time (baseline to 30 days)



- No quantifiable systemic exposure at any time point
- Local non-systemic therapy

Phase III: Double-blind Study Design

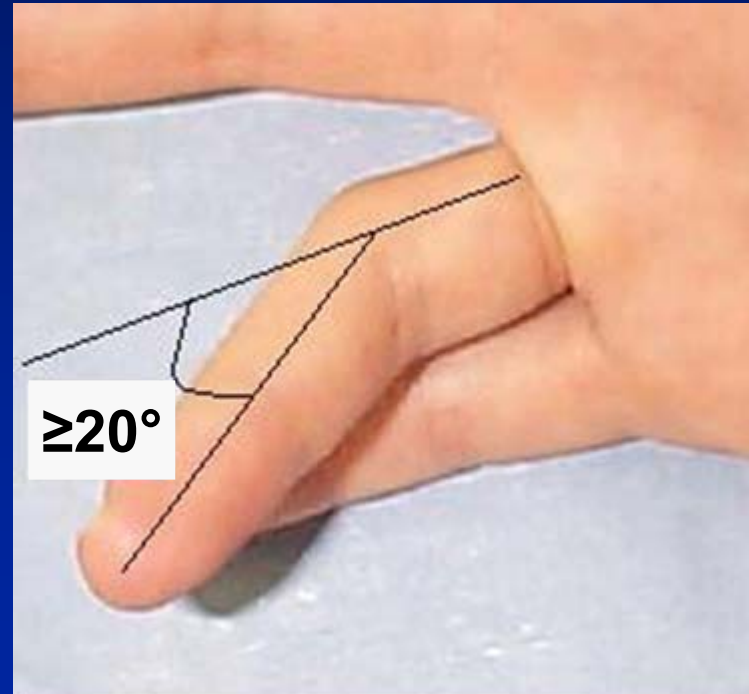
- AA4500 0.58 mg vs. placebo at each injection cycle



- Up to 3 injections per cord at 4 week intervals
- Primary outcome is reduction of contracture to 0-5° (normal extension)
- Followed by open-label extension phase

Phase III: Key Inclusion Criteria

- ≥ 18 years of age
- At least one affected joint with palpable cord and contracture of at least 20° and
 - MP = 20° - 100°
 - PIP = 20° - 80°



Phase III: Key Exclusion Criteria

- **Bleeding disorders or recent stroke**
- **Other disorders affecting the hand**
- **Previous treatment within 90 days of study start**
- **Tetracycline derivative use within 14 days**
- **Anticoagulant within 7 days (except LD Aspirin)**
- **Allergy to collagenase or its excipients**

Phase III: Efficacy Assessments and Design

- Efficacy Assessments:
 - Full extension
 - Full flexion
 - Range of Motion (ROM)
 - ROM = full flexion minus full extension
- Randomization 2:1 (AA4500:placebo)
 - Stratification
 - Joint type (MP or PIP)
 - Baseline severity contracture (Studies I and II)
 - MP: Low ($\leq 50^\circ$) vs. High ($> 50^\circ$)
 - PIP: Low ($\leq 40^\circ$) vs. High ($> 40^\circ$)

Phase III: Safety Assessments

- Adverse events
- Immunogenicity
- Laboratory
- Vital signs

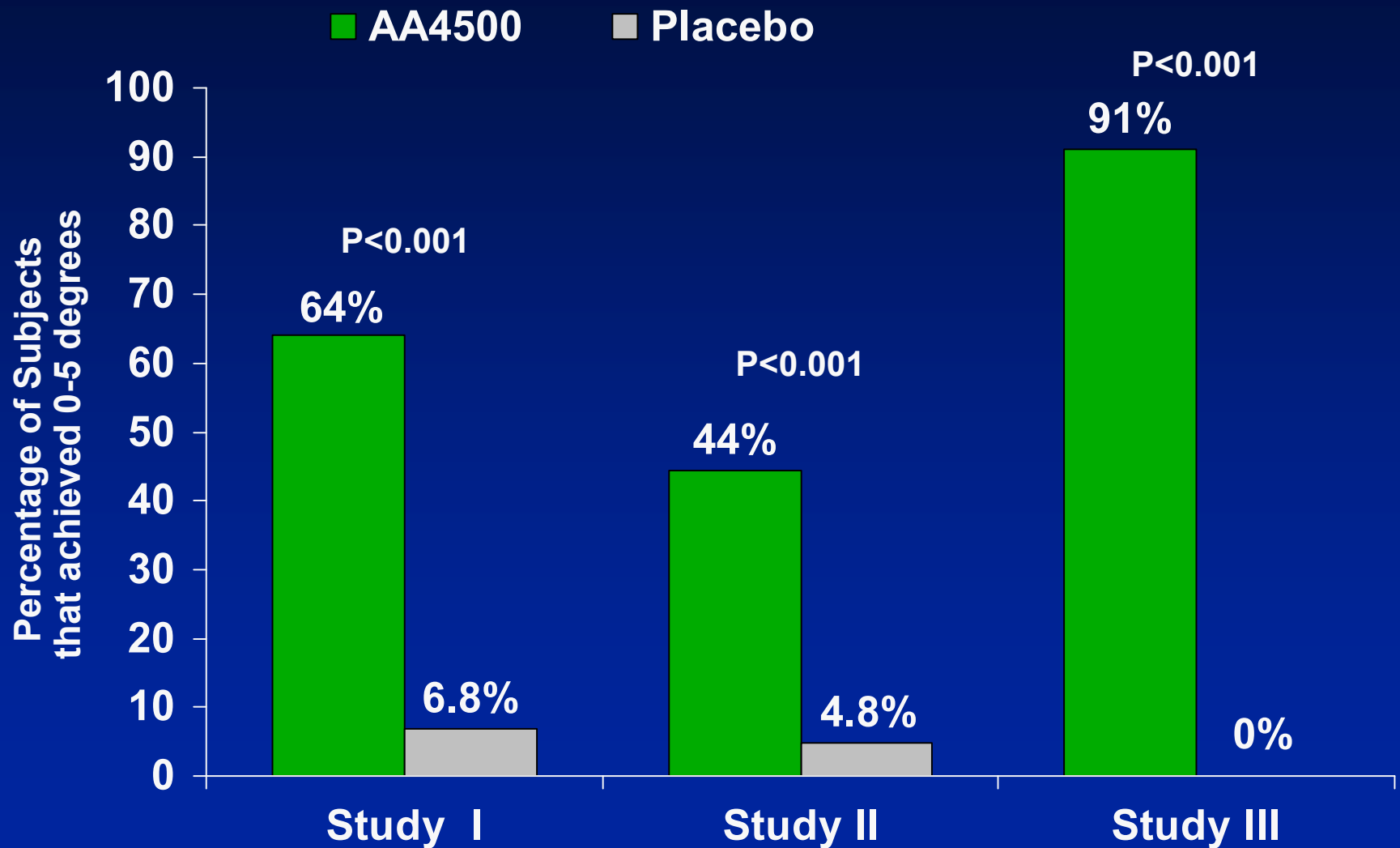
Phase III: Clinical Endpoints

- **Primary endpoint: Percentage of subjects achieving a correction to within 0-5° after last injection (clinical success)**
- **Multiple secondary endpoints**
 - % achieving $\geq 50\%$ reduction
 - % change from baseline contraction angle
 - Time to achieve clinical success
 - Change in range of motion
- **Additional outcomes**
 - Physician and Patient global assessments

Phase III: Disposition of Subjects

Study	AA4500 (N=271)	Placebo (N=136)
857 (I)	203	103
859 (II)	45	21
303 (III)	23	12
Completed Study	94.5%	96.3%
Male	84.9%	72.1%
Female	15.1%	27.9%
Age in years Mean (SD)	62.2 (9.2)	63.7 (9.5)

Results: Primary Endpoint Achieved in All 3 Studies



Phase III: Secondary Endpoint Hierarchy

	Last Injection			1 st Injection		
	All	MP	PIP	All	MP	PIP
Reduction in contracture to 5° or less	P					
Clinical improvement						
% change in contracture						
Time to reduction in contracture $\leq 5^\circ$						
Change in ROM						

Phase III: Secondary Endpoint Hierarchy

	Last Injection			1 st Injection		
	All	MP	PIP	All	MP	PIP
Reduction in contracture to 5° or less	P					
Clinical improvement	1					
% change in contracture	2					
Time to reduction in contracture $\leq 5^\circ$	3					
Change in ROM	4					

Phase III: Secondary Endpoint Hierarchy

	Last Injection			1 st Injection		
	All	MP	PIP	All	MP	PIP
Reduction in contracture to 5° or less	P	5				
Clinical improvement	1	6				
% change in contracture	2	7				
Time to reduction in contracture $\leq 5^\circ$	3	8				
Change in ROM	4	9				

Phase III: Secondary Endpoint Hierarchy

	Last Injection			1 st Injection		
	All	MP	PIP	All	MP	PIP
Reduction in contracture to 5° or less	P	5	10			
Clinical improvement	1	6	11			
% change in contracture	2	7	12			
Time to reduction in contracture $\leq 5^\circ$	3	8	13			
Change in ROM	4	9	14			

Phase III: Secondary Endpoint Hierarchy

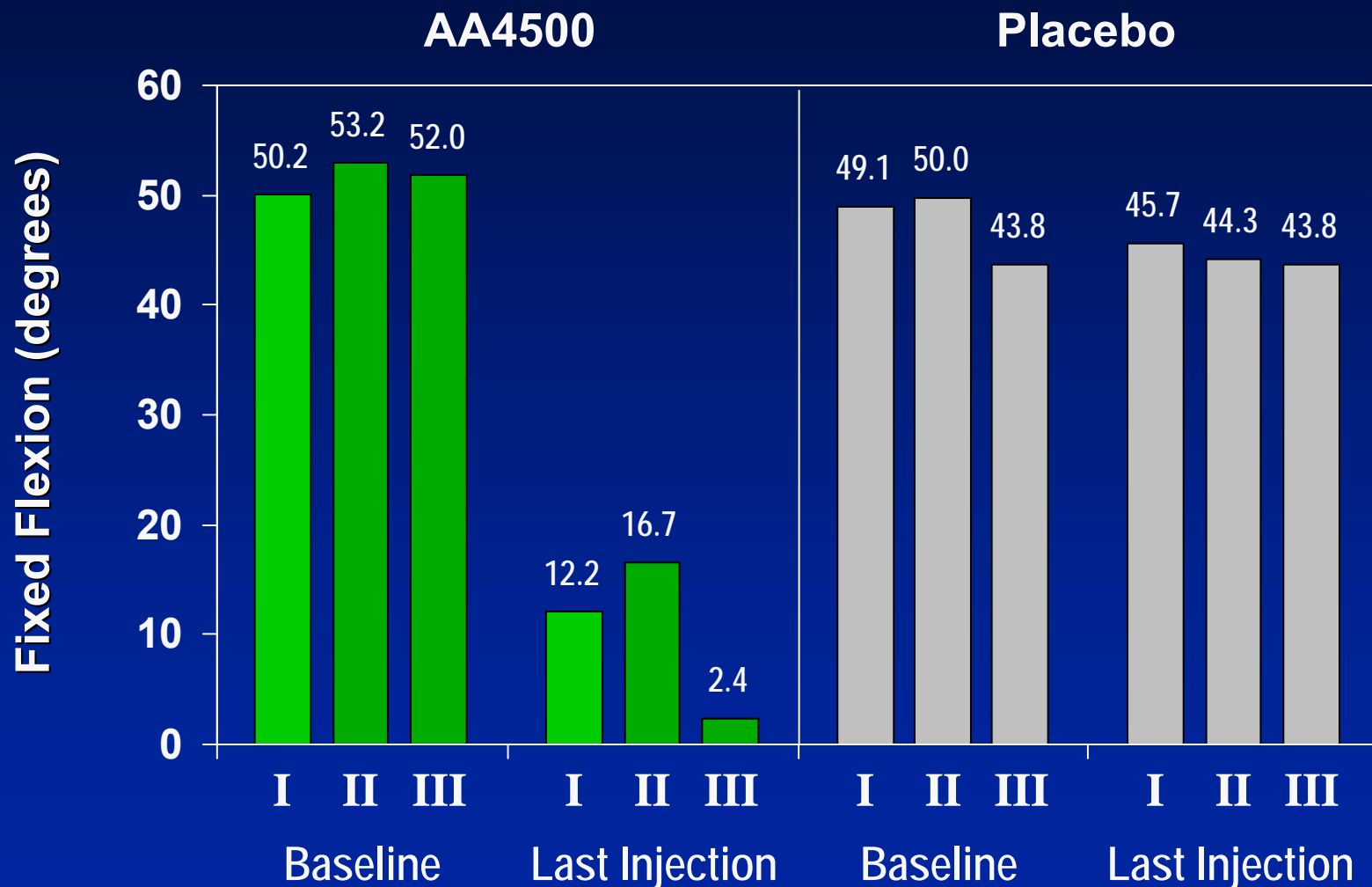
	Last Injection			1 st Injection		
	All	MP	PIP	All	MP	PIP
Reduction in contracture to 5° or less	P	5	10	15	19	23
Clinical improvement	1	6	11	16	20	24
% change in contracture	2	7	12	17	21	25
Time to reduction in contracture $\leq 5^\circ$	3	8	13	—	—	—
Change in ROM	4	9	14	18	22	26

Secondary Endpoints

Order	Parameter	Joint		Study I	Study II	Study III
1	Clinical improvement	All	Last inject	●	●	Not Measured
2	% change in contracture	All		●	●	●
3	Time to reduction in contracture to 5° or less	All		●	●	●
4	Change in ROM	All		●	●	●
5	Reduction in contracture to 5° or less	MP		●	●	●
6	Clinical improvement	MP		●	●	Not Measured
7	% change in contracture	MP		●	●	●
8	Time to reduction in contracture to 5° or less	MP		●	●	●
9	Change in ROM	MP		●	●	●
10	Reduction in contracture to 5° or less	PIP	First inject	●	NS	●
11	Clinical improvement	PIP		●	-	Not Measured
12	% change in contracture	PIP		●	-	●
13	Time to reduction in contracture to 5° or less	PIP		●	-	●
14	Change in ROM	PIP		●	-	●
15	Reduction in contracture to 5° or less	All		●	-	●
16	Clinical improvement	All		●	-	Not Measured
17	% change in contracture	All		●	-	●
18	Change in ROM	All		●	-	●
19	Reduction in contracture to 5° or less	MP	First inject	●	-	●
20	Clinical improvement	MP		●	-	Not Measured
21	% change in contracture	MP		●	-	●
22	Change in ROM	MP		●	-	●
23	Reduction in contracture to 5° or less	PIP		●	-	●
24	Clinical improvement	PIP		●	-	Not Measured
25	% change in contracture	PIP		●	-	●
26	Change in ROM	PIP		●	-	-

Clinical Efficacy – Degree of Contracture

Fixed Flexion



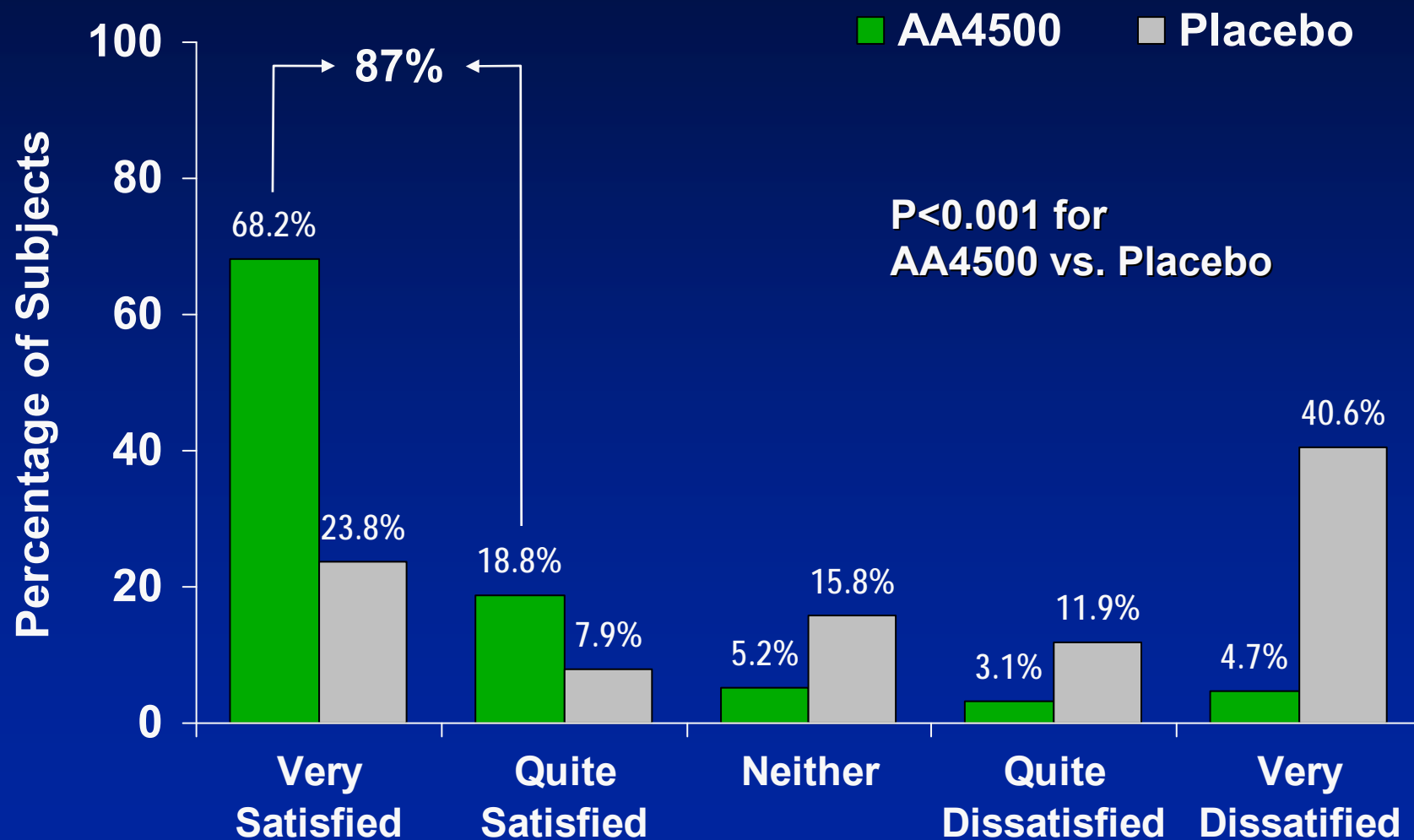
Efficacy Results: Mean Change in Range of Motion (°)

	(Study I)		(Study II)	
	AA4500	Placebo	AA4500	Placebo
	N=197	N=102	N=45	N=21
All Primary				
Baseline ROM				
Mean (SD)	43.9° (20.1)	45.3° (18.7)	40.3° (15.2)	44.0° (16.5)
Day 30 ROM				
Mean (SD)	80.7° (19.0)	49.5° (22.1)	75.8° (17.7)	51.7° (19.6)
Mean increase in ROM	36.7°	4.0°	35.4°	7.6°
p-value ^a	<0.001	—	<0.001	—

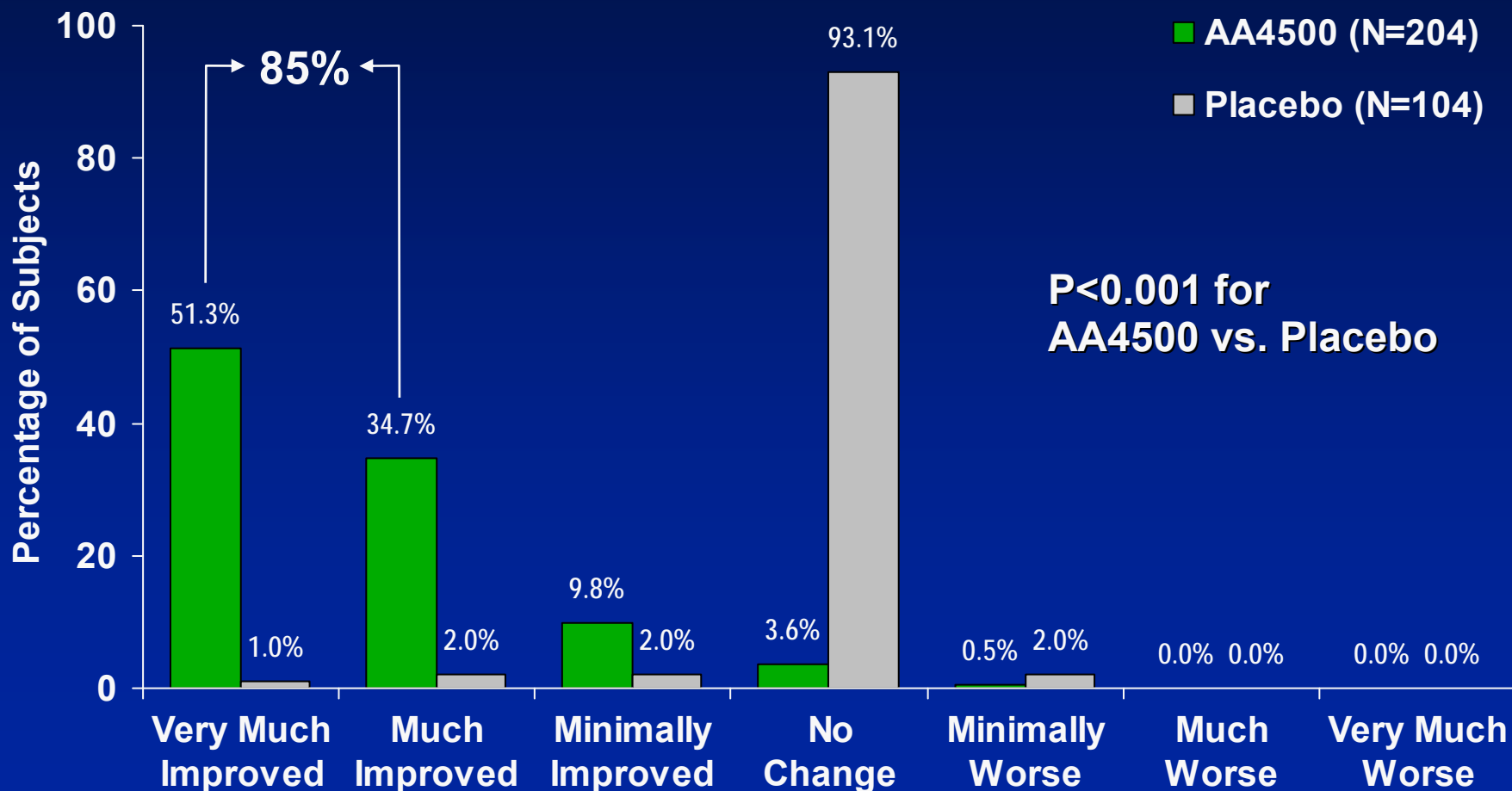
ROM=range of motion.

^a p-value based on full factorial model ANOVA with treatment group, joint type, and baseline severity as factors.

Patient Assessment: Treatment Satisfaction



Physician Assessment: Improvement of Dupuytren's Disease



AA4500: Durability of Response

- **830 successfully treated joints**
- **30 (4%) had recurrence of contracture**
 - **50% occurred between 3-6 months of follow up**
- **Mean follow up period was 7.4 months**

AUX-CC-860

2 to 5 Year Long-term Observational Follow-up Study

- **To assess the durability of response in joints with measurable improvement ($\geq 20^\circ$) in contracture after treatment with AA4500**
- **To assess the progression of disease**
 - **In joints that were not treated, or**
 - **Did not have measurable improvement ($< 20^\circ$) after treatment**

AA4500: Summary of Efficacy

- **All studies met primary endpoint**
 - **Significantly more AA4500 subjects achieved a reduction to 0-5 degrees than placebo subjects**
- **Multiple secondary endpoints, including improvement in range of motion, provide supportive evidence of efficacy**
- **Patient & physician satisfaction significantly better for AA4500 compared to placebo**
- **Provides efficacy comparable to surgical correction**

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AA4500: Safety Profile

James Tursi, MD

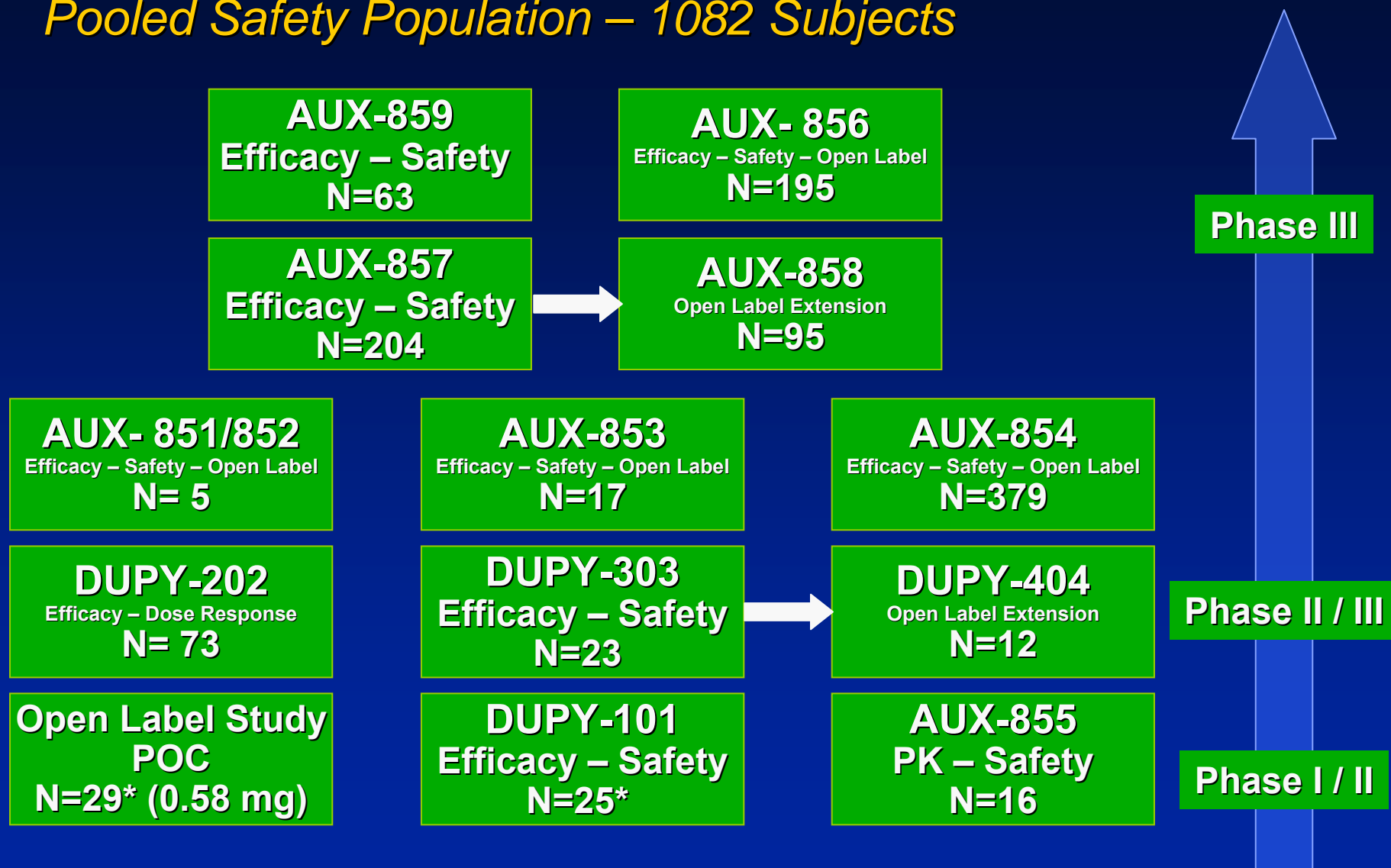
*Vice President, Clinical Affairs
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Introduction

- **AA4500 Safety database overview**
 - Disposition
 - Extent of exposure
 - Duration of follow-up
- **Adverse events**
 - Local
 - Serious adverse event (SAE)
 - Additional safety parameters
- **Immunogenicity profile**

AA4500 Clinical Development Program

Pooled Safety Population – 1082 Subjects



*No formal safety data base

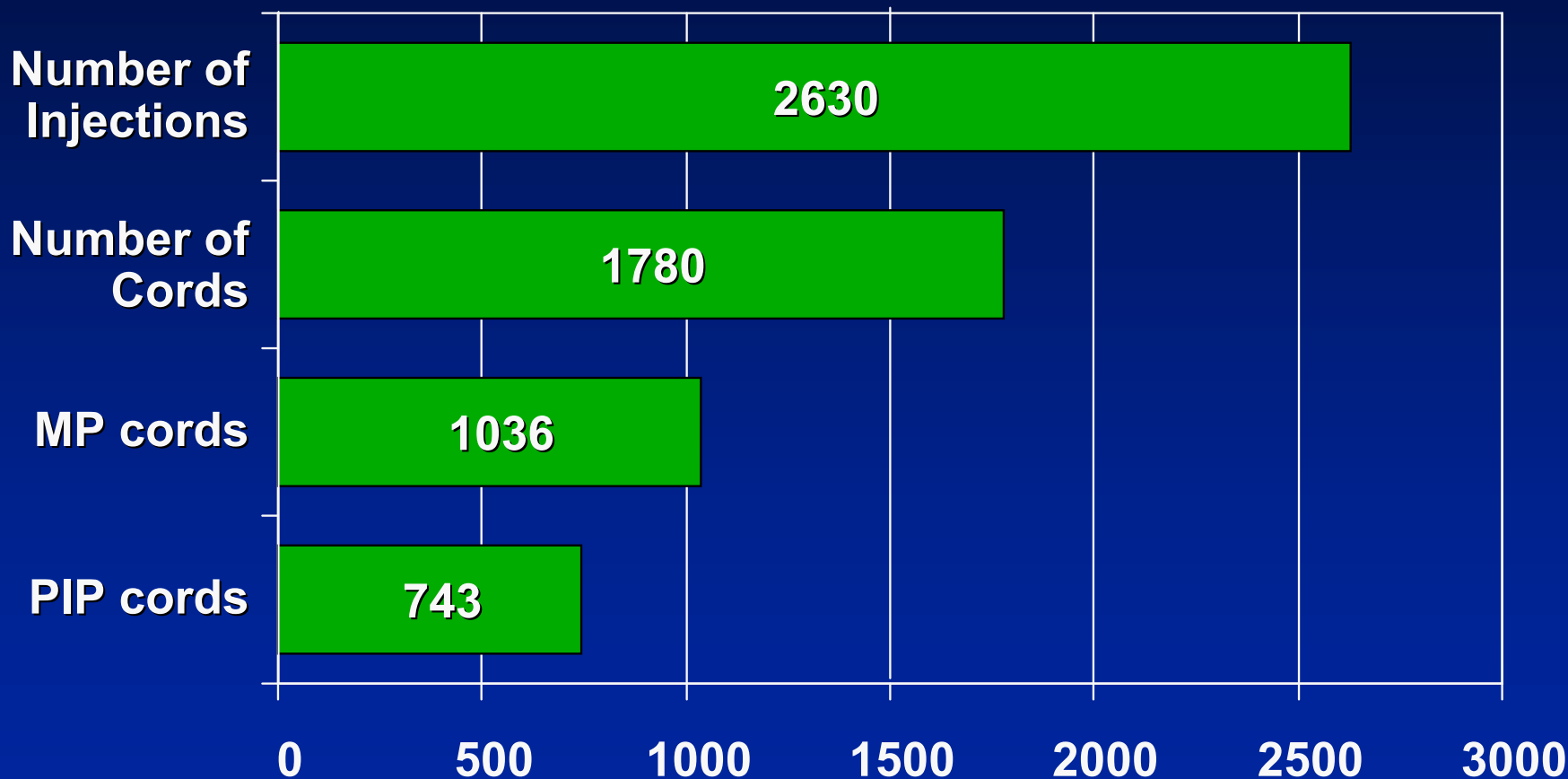
Subject Disposition

1082 Subjects with at Least 1 Dose of AA4500 0.58 mg

- **87.6% completed**
- **12.4% discontinued**
 - **Most common reasons**
 - **Lost to follow-up**
 - **Withdrew consent**
- **Subjects age ranged from 33 to 90 years**
- **May have received from 1 to 8 injections**

Extent of Exposure

1082 Subjects with at Least 1 Dose of AA4500 0.58 mg



Note: Single DIP joint treated in DUPY-202

Duration of Patient Follow-up from 1st Injection

All Subjects with at Least 1 Dose of AA4500 0.58 mg

Overall Duration	AA4500 0.58 mg (N=1082)
Mean (SD)	9.5 (4.6) Months
Median	9.0 Months
Min, Max	2 Days , 6.7 Years

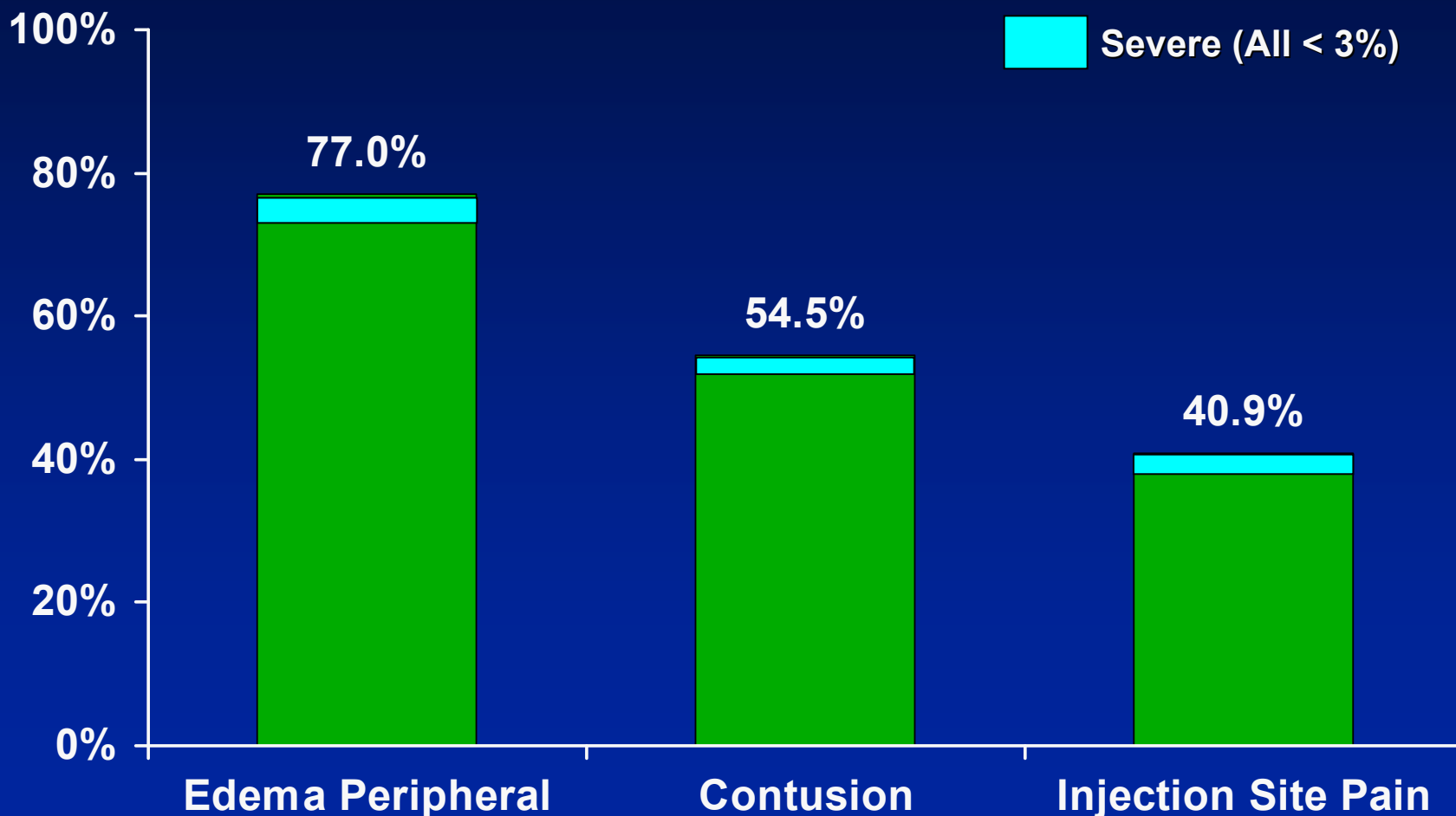
Inter-injection interval ranged from 10 days to > 6.4 Years

AA4500

Adverse Events

Most Common Adverse Events ($\geq 5\%$)

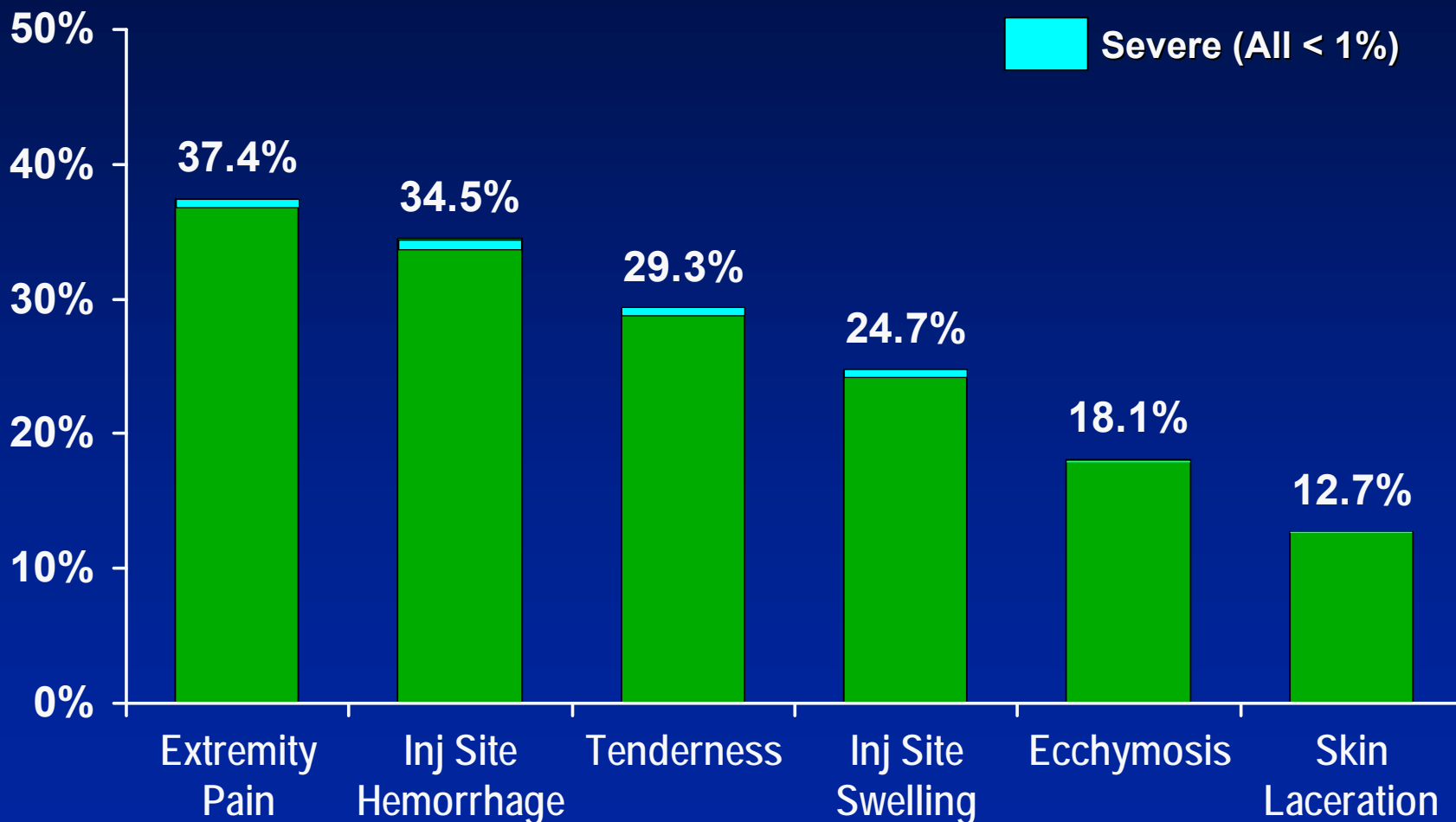
Safety Population – AA4500 First Dose to End of Study



N=1082

Adverse Events ($\geq 5\%$)

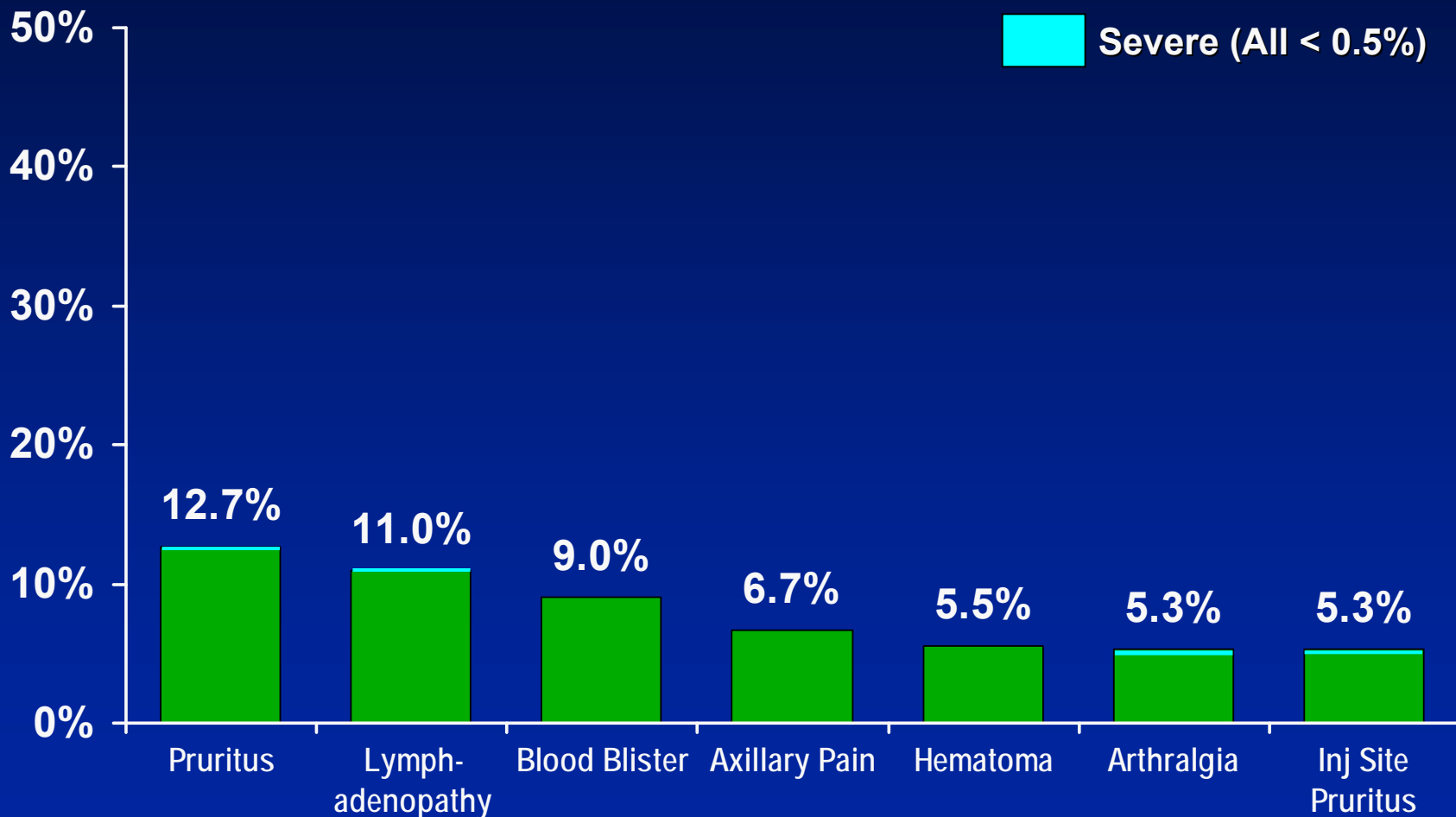
Safety Population – AA4500 First Dose to End of Study



N=1082

Adverse Events ($\geq 5\%$)

Safety Population – AA4500 First Dose to End of Study



N=1082

AA4500 Adverse Events

Trends

- **Confined to the treated extremity**
- **Non-serious / mild or moderate intensity**
- **Resolution before the next injection without intervention**
 - **Median duration of all AEs → 10 Days**

AA4500

Serious Adverse Events

AA4500 Serious Adverse Events

- 92 (8.5%) Subjects experienced non-fatal SAEs
- If SAE did not involve the treated extremity - similar proportion of AA4500 and placebo subjects
- 9 subjects with 10 SAEs considered treatment related (TR)
 - Ligament injury
 - Flexor tendon rupture (3)
 - Complex regional pain syndrome
 - Boutonniere Deformity
 - Deep vein thrombosis
 - Sensory disturbance†
 - Dupuytren's contracture†
 - Tendonitis

† Same subject experienced both SAEs

Serious Adverse Events

Ligament Injury / Tendon Rupture Details

Subject Age	Injection Number	Details	Type of Injury / Repair
61M	2	Day 43 – Worsening finger function PE - significant bowstringing	Ligament injury (A2 and A4 Pulley Rupture) Joint fusion and tenotomy performed
62M	1	Day 6 – Finger weakness PE and MRI confirmed Pre-existing boutonnière deformity	FDS tendon rupture FDP intact DIP Joint fusion performed
61M	1	Day 8 – Lifted heavy pallet Immediate finger swelling / weakness MRI confirmed rupture	FDP tendon rupture Partial FDS tear Tenolysis performed
76M	3	Day 4 – Inability to flex PE confirmed	FDS and FDP tendon rupture Two stage repair with tendon grafting procedure

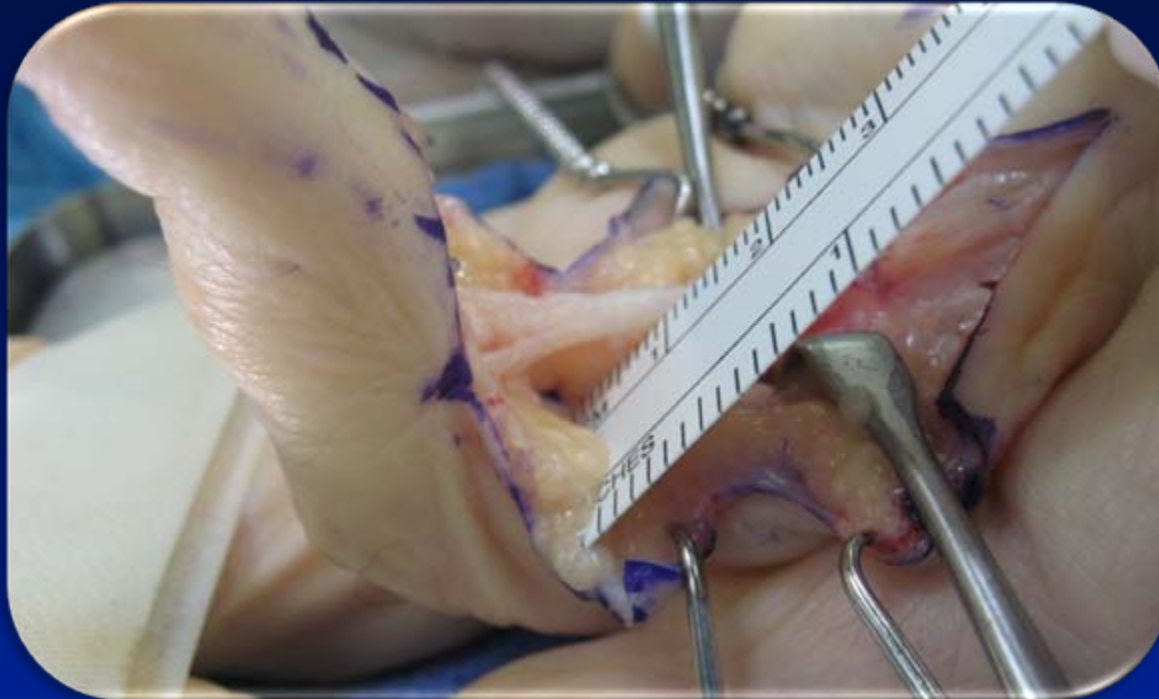
FDS – Flexor digitorum superficialis

FDP – Flexor digitorum profundus

N=1082

Ligament Damage / Tendon Ruptures

Understanding Dupuytren's Anatomy



- Tendon and Dupuytren's cord are in close proximity
- Considered related to effect of AA4500
- A focus of the risk management plan

AA4500

Additional Safety Parameters

Abnormal Laboratory Values – Chemistry

Percentage Low and Comparable to Placebo

Subjects With At Least 1 Dose of AA4500 0.58 mg and Placebo

Laboratory Parameter	SI Criteria	AA4500 0.58 mg N=974		Placebo* N=125	
		n	N (%)	n	N (%)
BUN	CS+: ≥ 35 mg/dL	925	9 (1.0)	120	1 (0.8)
Creatinine	CS+: ≥ 3.0 mg/dL	925	0 (0.0)	120	0 (0.0)
ALT (U/L)	CS+: $> 3 \times \text{ULN}$	924	6 (0.7)	120	1 (0.8)
AST (U/L)	CS+: $> 3 \times \text{ULN}$	923	6 (0.7)	120	1 (0.8)

* Reflects 90 day period of double-blind placebo-controlled trial only

Abnormal Laboratory Values – Hematology

Percentage Low and Comparable to Placebo

Subjects With At Least 1 Dose of AA4500 0.58 mg and Placebo

Laboratory Parameter	SI Criteria	AA4500 0.58 mg N=974		Placebo* N=125	
		n	N (%)	n	N (%)
Hematocrit	CS-: $\leq 30\%$	924	1 (0.1)	120	0 (0.0)
Hemoglobin	CS-: ≤ 10 g/dL (F)	927	4 (0.4)	120	0 (0.0)
	≤ 11 g/dL (M)				
Platelets	CS+: ≥ 650 $10^3/\mu\text{L}$	923	1 (0.1)	120	0 (0.0)
	CS-: ≤ 100 $10^3/\mu\text{L}$	923	4 (0.4)	120	0 (0.0)

* Reflects 90 day period of double-blind placebo-controlled trial only

Vital Sign Parameter Changes

Similar to Placebo

Vital Sign	Criteria	AA4500 0.58 mg (N=1082) n (%)	Placebo* (N=137) n (%)
Systolic blood pressure	Increase	118 (10.9)	12 (8.8)
	Decrease	31 (2.9)	5 (3.6)
Diastolic blood pressure	Increase	99 (9.1)	8 (5.8)
	Decrease	36 (3.3)	10 (7.3)
Heart rate	Increase	9 (0.8)	2 (1.5)
	Decrease	43 (4.0)	4 (2.9)
Respiratory rate	Increase	13 (1.2)	2 (1.5)
	Decrease	6 (0.6)	2 (1.5)
Temperature	Increase	3 (0.3)	0 (0.0)

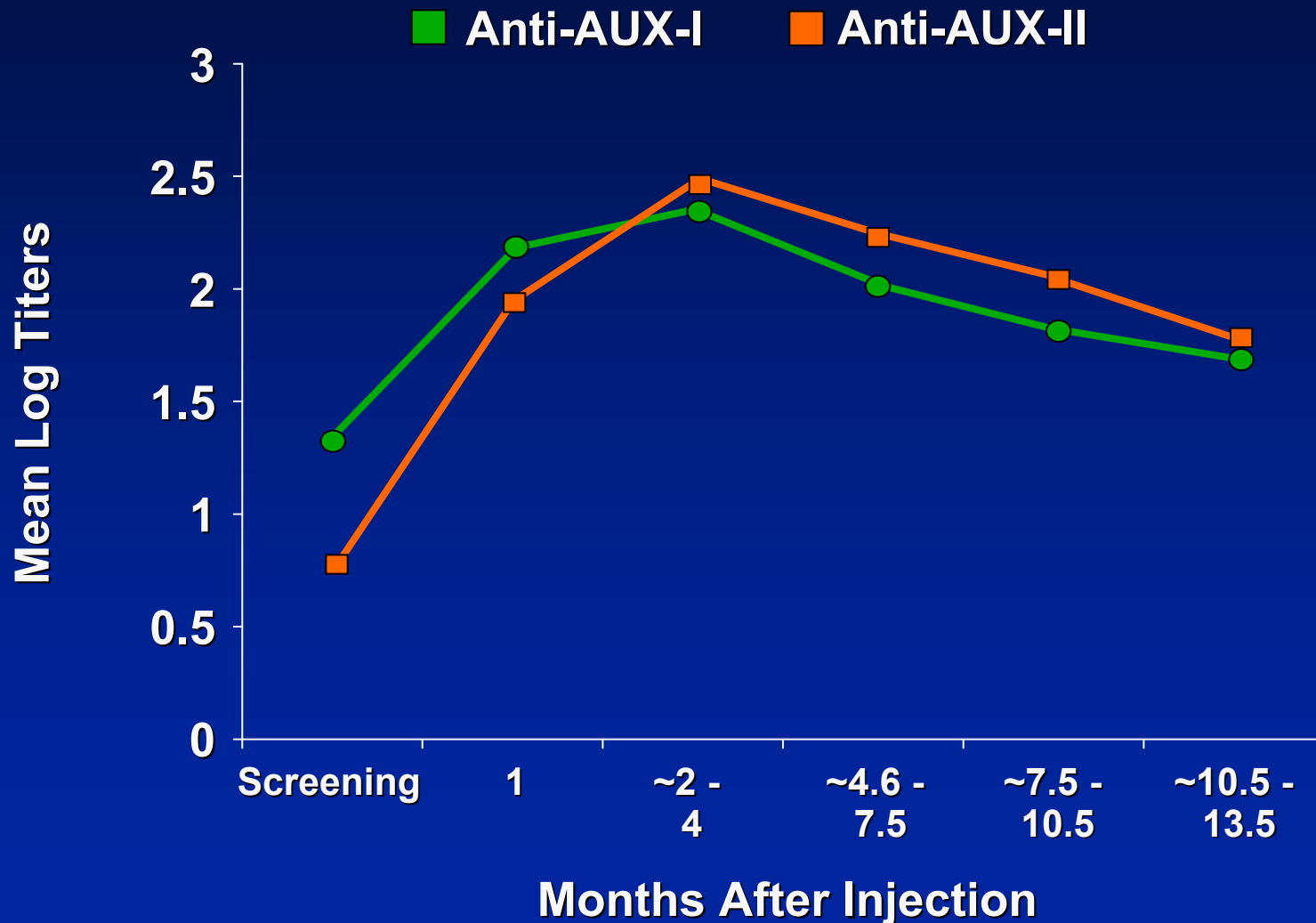
* Reflects 90 day period of double-blind placebo-controlled trial only

AA4500

Immunogenicity

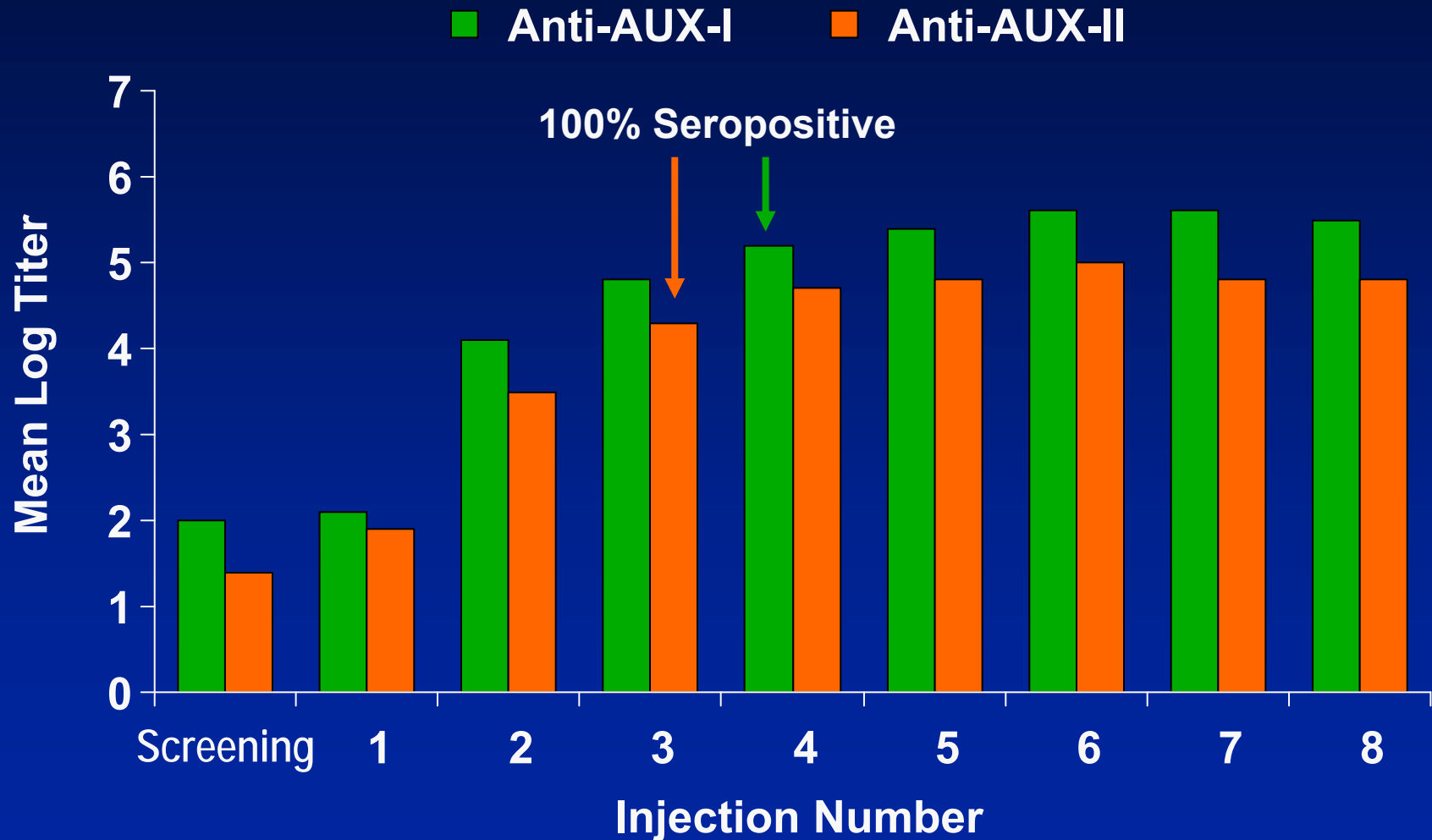
Anti-AUX-I and Anti-AUX-II Titers

Single AA4500 Injection – Waning Over Time



Anti-AUX-I and Anti-AUX-II Antibody Titers

By Injection Number



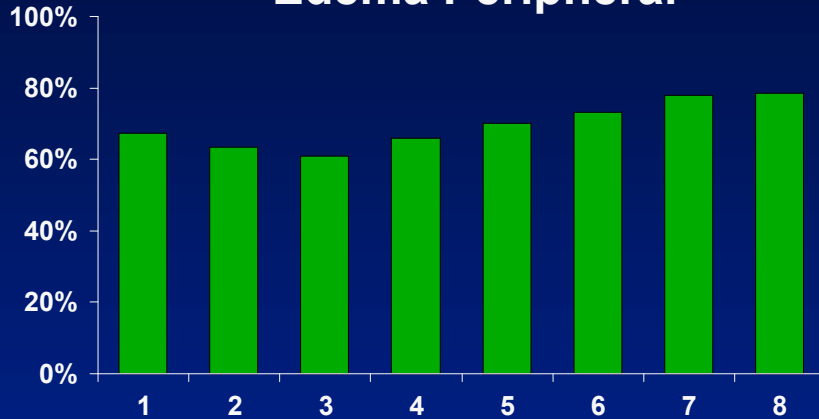
Antidrug Antibodies

Do Antibodies Affect Safety?

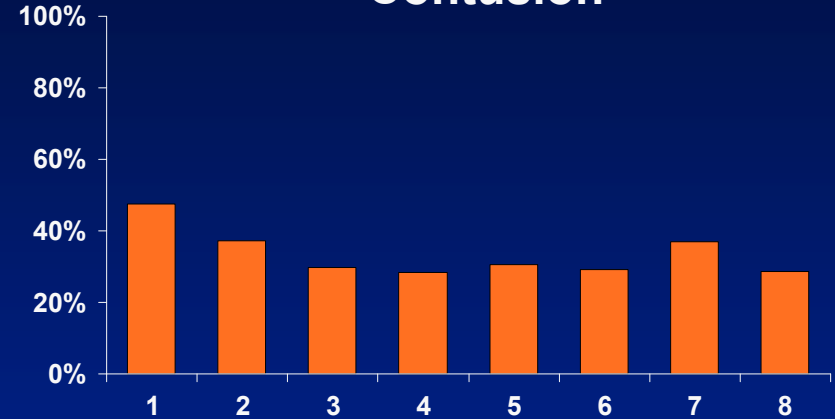
- **Rate of adverse events**
- **Severity of adverse events**
- **Duration of adverse events**
- **Systemic anaphylactic reactions**

Most Common Adverse Event Rates by Injection Number

Edema Peripheral



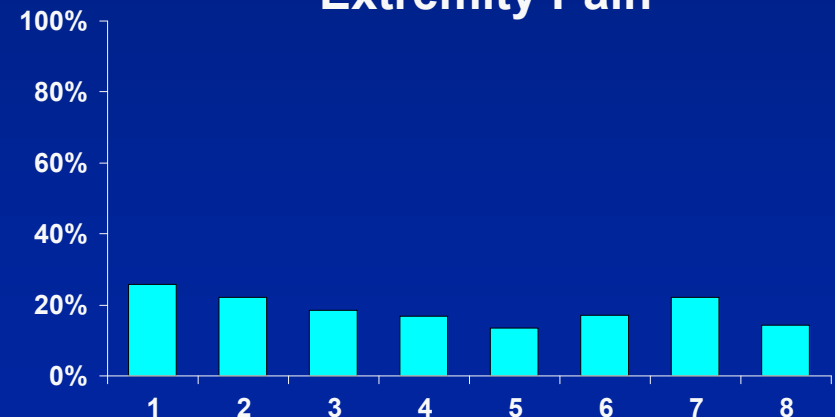
Contusion



Injection Site Pain



Extremity Pain



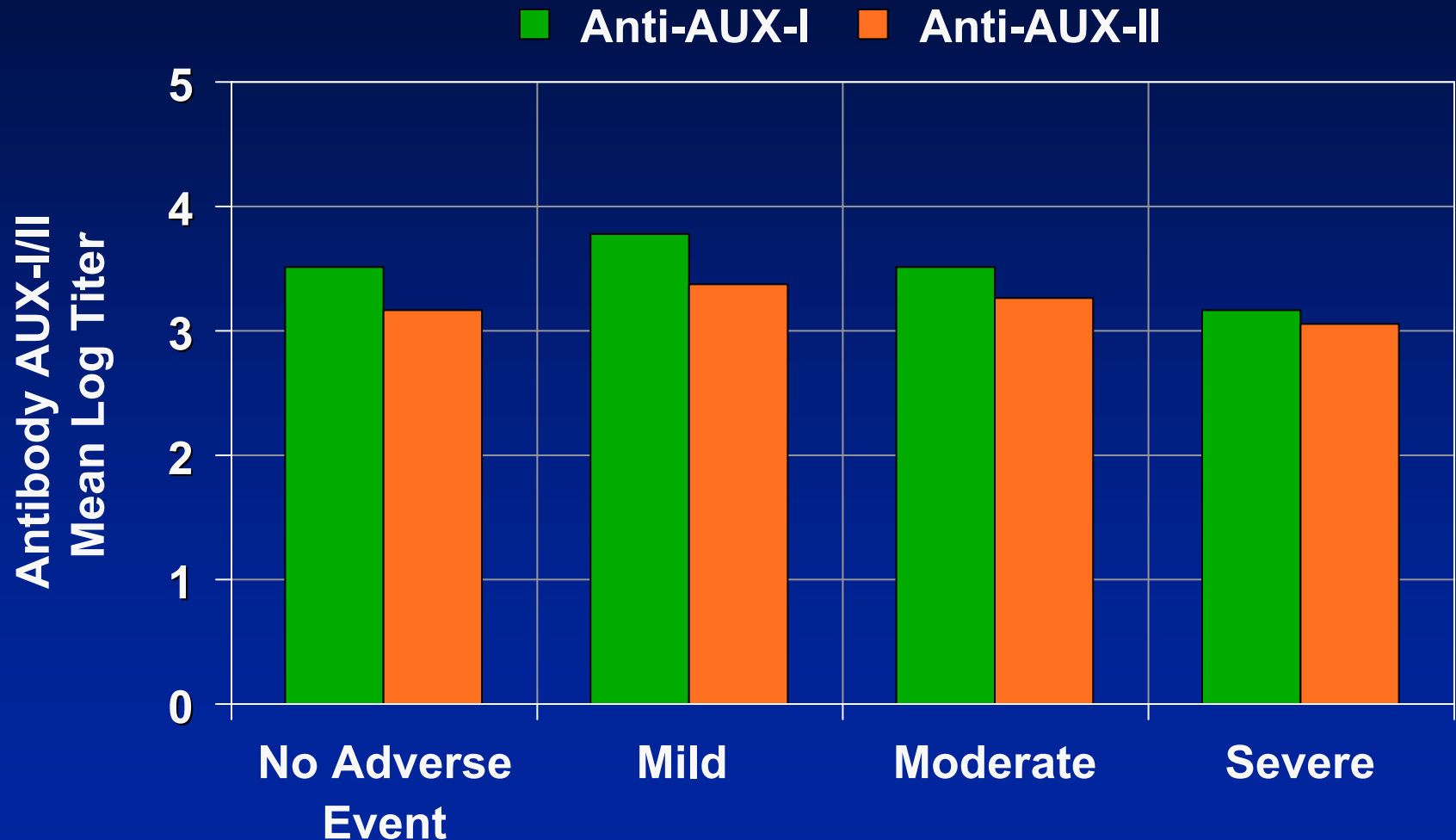
Antidrug Antibodies

Do Antibodies Affect Safety?

- **Rate of adverse events**
 - **No consistent pattern demonstrated between adverse event rates and increasing antibody titers**
- **Severity of adverse events**
- **Duration of adverse events**
- **Systemic anaphylactic reactions**

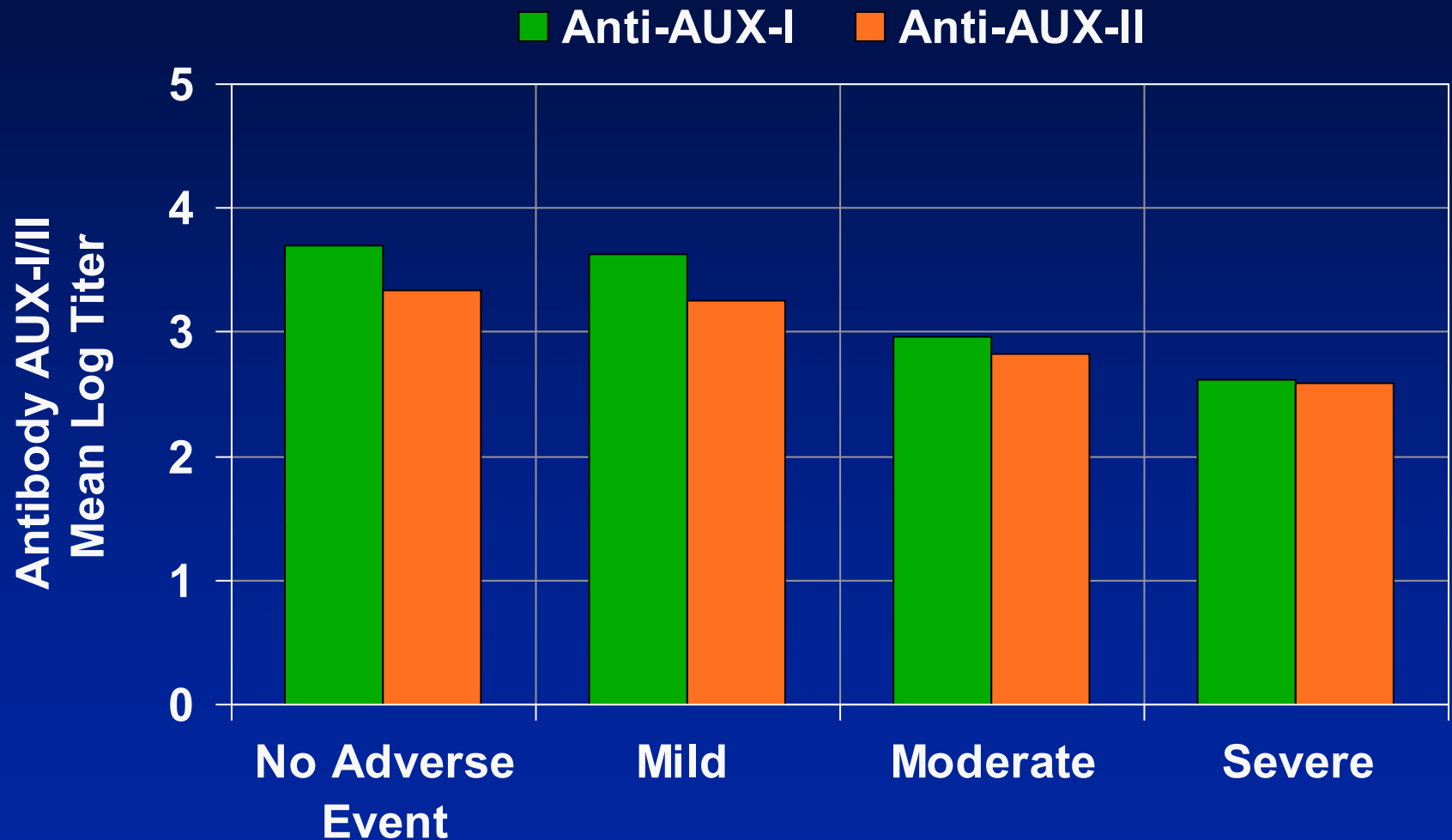
Edema Peripheral

Anti-AUX-I / II Antibody Titer and Adverse Event Severity



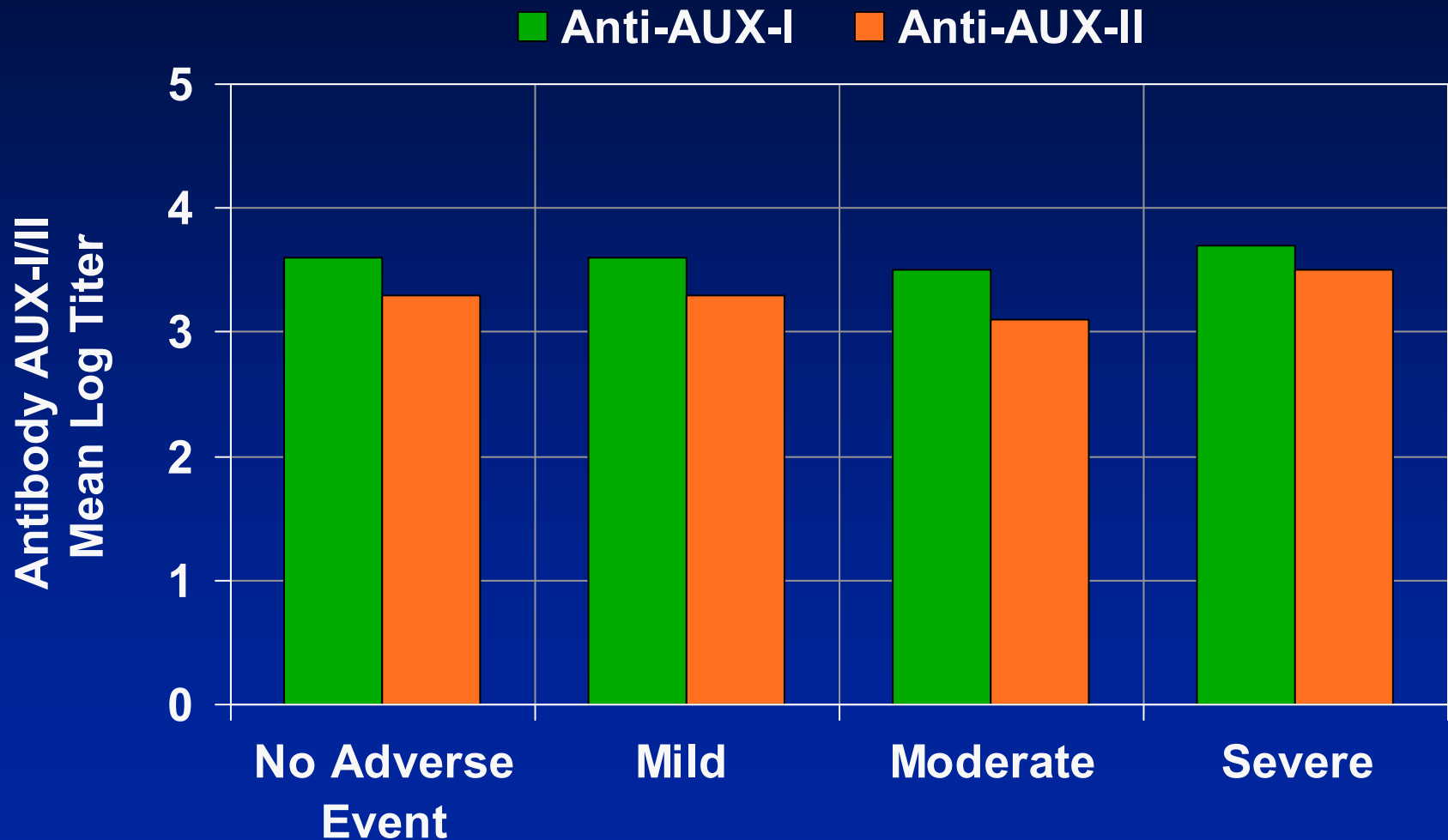
Contusion

Anti-AUX-I / II Antibody Titer and Adverse Event Severity



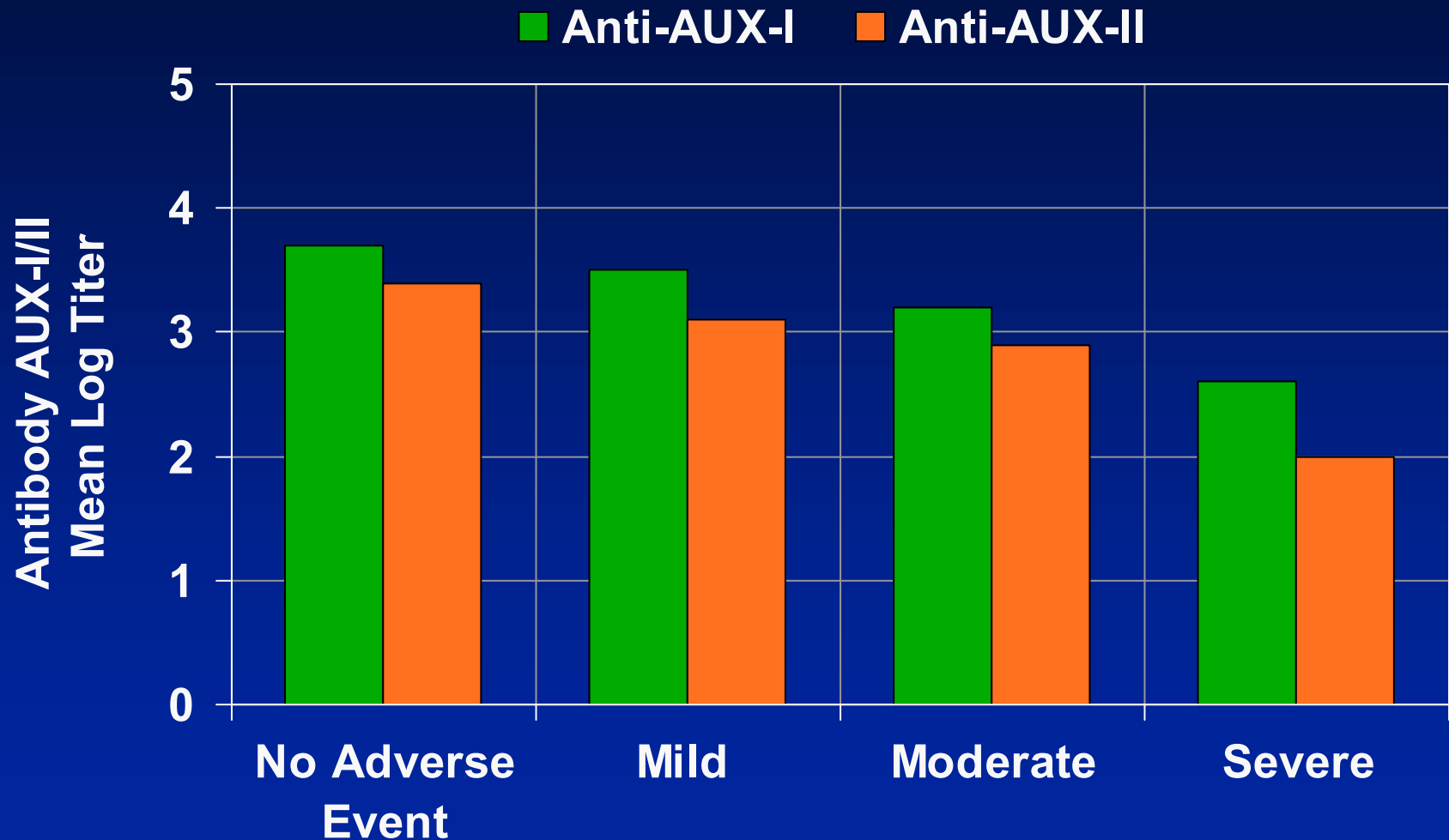
Injection Site Pain

Anti-AUX-I / II Antibody Titer and Adverse Event Severity



Extremity Pain

Anti-AUX-I / II Antibody Titer and Adverse Event Severity



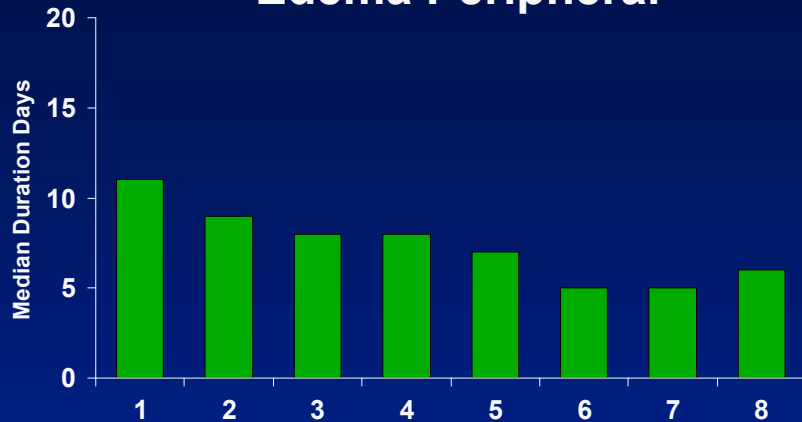
Antidrug Antibodies

Do Antibodies Affect Safety?

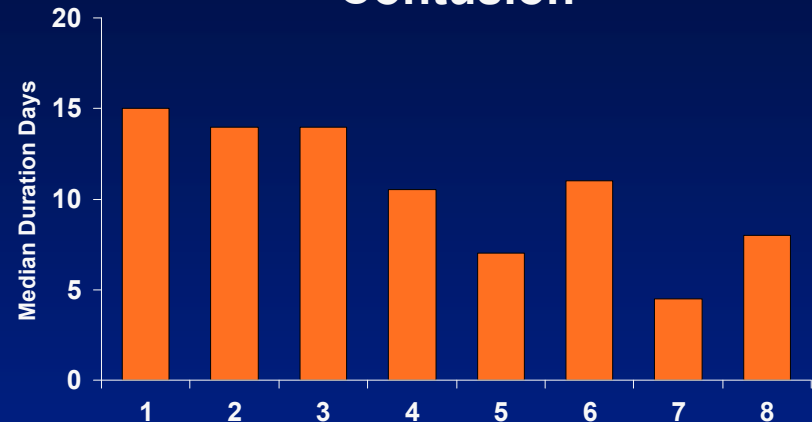
- **Rate of adverse events**
- **Severity of adverse events**
 - **Adverse event severity does not correlate with antibody titer**
- **Duration of adverse events**
- **Systemic anaphylactic reactions**

Most Common Adverse Event Duration by Injection Number – Median Days

Edema Peripheral



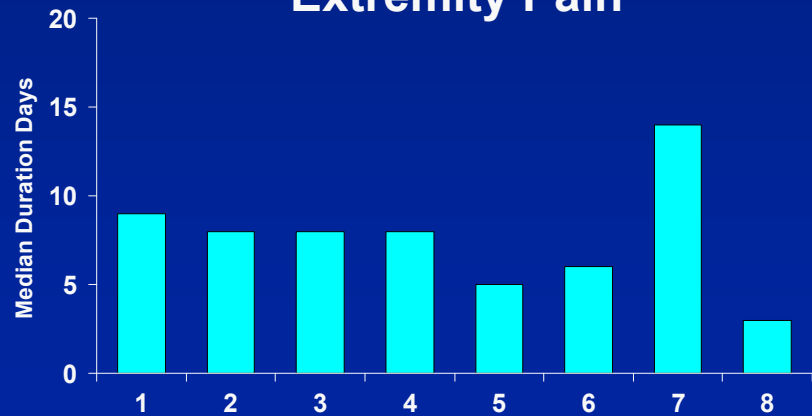
Contusion



Injection Site Pain



Extremity Pain



Antidrug Antibodies

Do Antibodies Affect Safety?

- **Rate of adverse events**
- **Severity of adverse events**
- **Duration of adverse events**
 - The duration of adverse events does not correlate with subsequent injections and increasing antibody titers
- **Systemic anaphylactic reactions**
 - None

AA4500

Safety Summary

AA4500 Safety Summary

Safety Database of 1082 Patients – 2630 Injections

- **Most frequent adverse events**
 - Confined to the treated extremity, mild or moderate in intensity resolving before the next injection
- **Serious adverse events**
 - Tendon rupture / ligament injury risk identified
 - Focus of Risk Management Plan

AA4500 Safety Summary (cont.)

Safety Population of 1082 Patients

- **Routine labs / vital signs with no clinically meaningful differences between AA4500 and placebo**
- **Antibodies develop in nearly all subjects but do not appear to affect safety profile**
- **No events / signals indicative of systemic anaphylaxis in the clinical program**

AA4500: Risk Management Activities

Risk Management Plan – Goals

Ensure Appropriate Administration of AA4500

- **Recognize potential and identified risks**
- **Creation and implementation of strategies to minimize those risks**
- **Information and education for physicians and patients**

Potential and Identified Safety Concerns

- **Potential risks**
 - Injection-related bleeding in subjects with coagulation disorders
 - Allergic reactions
- **Identified tolerability / safety concerns**
 - Localized reactions
 - Tendon rupture and ligament damage

Potential Risks

Risk Management

Potential Risks

Risk Management Activities – Labeling

- **Injection-related bleeding in subjects with coagulation disorders**
 - Caution with coagulation disorders
 - Not recommended with concurrent anticoagulant medications
 - Prophylactic low-dose aspirin use acceptable in clinical program
- **Allergic reactions**
 - Contraindication with known hypersensitivity
 - Prepare to address any allergic reactions

Identified Tolerability /
Safety Concerns
Risk Management

Localized Reactions

Common and Expected with AA4500 Treatment

- **Most common**
 - Edema peripheral
 - Contusion
 - Injection site pain
- **Mild or moderate with resolution before the next injection without intervention**
- **Physicians and patients should know what to expect from AA4500**

Localized Reactions

Risk Management Activities

- **Product Labeling**
 - Local reactions are identified
 - Multiple cords should not be treated simultaneously
 - One hand treated per session
- **Physician training**
 - Include details of local reactions
- **Patient product information**
 - Local reactions described

Tendon Rupture and Ligament Damage

- Four cases in the safety population of 1082 subjects
- Inappropriate exposure to normal collagen-containing structures
 - Lysis of collagen and subsequent damage
 - Possible injury / reduction of functionality

Tendon Rupture and Ligament Damage

Risk Management Activities

- **Product labeling**
- **Physician Training Program**
- **Access Management Program**
- **Safety monitoring**
- **Patient education**

AA4500 Product Labeling

Detailed and Informative

- **Intended Users – *Physicians experienced in the diagnosis and management of Dupuytren's disease***
 - Hand surgeons
 - Orthopedic surgeons
 - Plastic surgeons
 - General surgeons (hand focus)
 - Rheumatologists
- **Tendon rupture risk identified**
- **Injection precaution**

AA4500 Product Labeling

Specific Precaution

Because AA4500 lyses collagen, care should be taken to avoid injecting into normal collagen-containing structures of the hand.

Exposure of collagen-containing structures to AA4500 may result in damage to those structures, and possible permanent injury such as tendon rupture or ligament damage.

Tendon Rupture and Ligament Damage

Risk Management Activities

- Product labeling
- **Physician Training Program**
- Access Management Program
- Safety monitoring
- Patient education

Physician Training – History

Challenges in the Clinical Program

- **New therapeutic procedure for advanced Dupuytren's disease**
- **Limited experience with AA4500**
- **Embarking on a multinational Phase III program**
- **Need to create a training program which could be extrapolated to multiple investigators**

AA4500 Injection Training

Investigator Training Options

- **Provided several options**
 - **Injection training workshop**
 - **Injection training at the investigator meeting**
 - **Injection training DVD or Injection Training Manual**
- **Found variability as to the preferred method of training for primary and sub-investigators**

Investigator Training Opportunities

Primary and Sub-Investigators – AUX-CC-857 / 859

	Injection Training Workshop	Injection Training (Investigator Meeting)	Training DVD or Manual or Observation
Primary Investigators (N=21)			
Sub- Investigators (N=20)			

AA4500 Physician Training

Evolution of the Proposed Physician Training Program

- **Met with investigators and other practicing physicians**
 - Included Hand Surgeons, Orthopedic Surgeons, Plastic Surgeons, Rheumatologists
 - Reviewed previous training methodologies
 - Discussed training needs and preferences
- **They requested a video / written training program**
 - Clear and comprehensive
 - Informative and accessible
 - Expanded from the clinical program

AA4500 Physician Training

Broader in Scope and Content than the Clinical Program

- **Will include additional information to help physicians use AA4500 appropriately**
- **Will provide more depth, examples, animations and demonstrations based on the experience of the clinical investigators**
- **Completion of training with attestation requirement “mandatory”**
- **Required before access to AA4500**

AA4500 Physician Training Program

Injection Training Video and Injection Manual

- **Program Components**
 - **Anatomy and pathology**
 - **Product preparation / injection / finger extension demonstrations**
 - **Frequently asked questions**
 - **Self assessment**
- **Created with and featuring demonstrations of appropriate use by physicians with experience using AA4500**
- **Hard copy training manual**

Physician Training Program Component

Review of Anatomy and Dupuytren's Pathology

- **Detailed illustrations**
 - Visualize the relationship of the Dupuytren's cord and other hand structures
- **Information on disease progression**
- **Mechanism of action of AA4500**
 - Better understand the treatment procedure

Physician Training Program Component

Demonstration of Injection / Finger Extension

- **Product preparation**
- **Needle placement**
 - Specific to the joint affected
- **Injection procedure**
- **Detailed description of the extension procedure**
 - Visualization of cord rupture

Physician Training Program Component

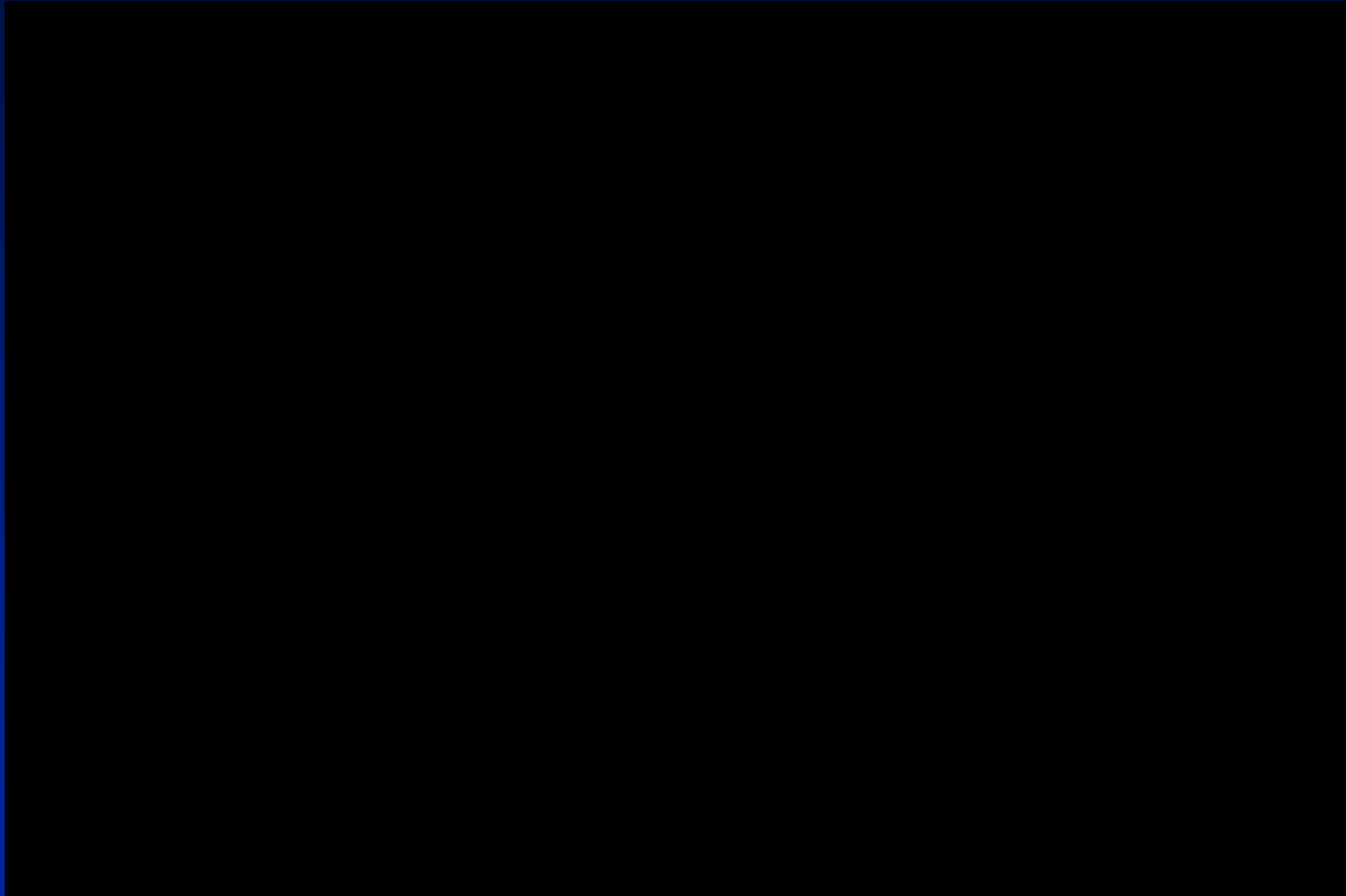
Frequently Asked Questions and Self Assessment

- **Product and procedure specific**
 - Preparation
 - Injection
 - Finger extension
- **Potential and identified risks discussed**
 - Local reactions / Tendon rupture
 - Adverse event reporting
- **Self assessment questions to ensure understanding of the content**

Injection Training Video – Injection



Injection Training Video – Extension



Tendon Rupture and Ligament Damage

Risk Management Activities

- Product labeling
- Physician Training Program
- **Access Management Program**
- Safety monitoring
- Patient education

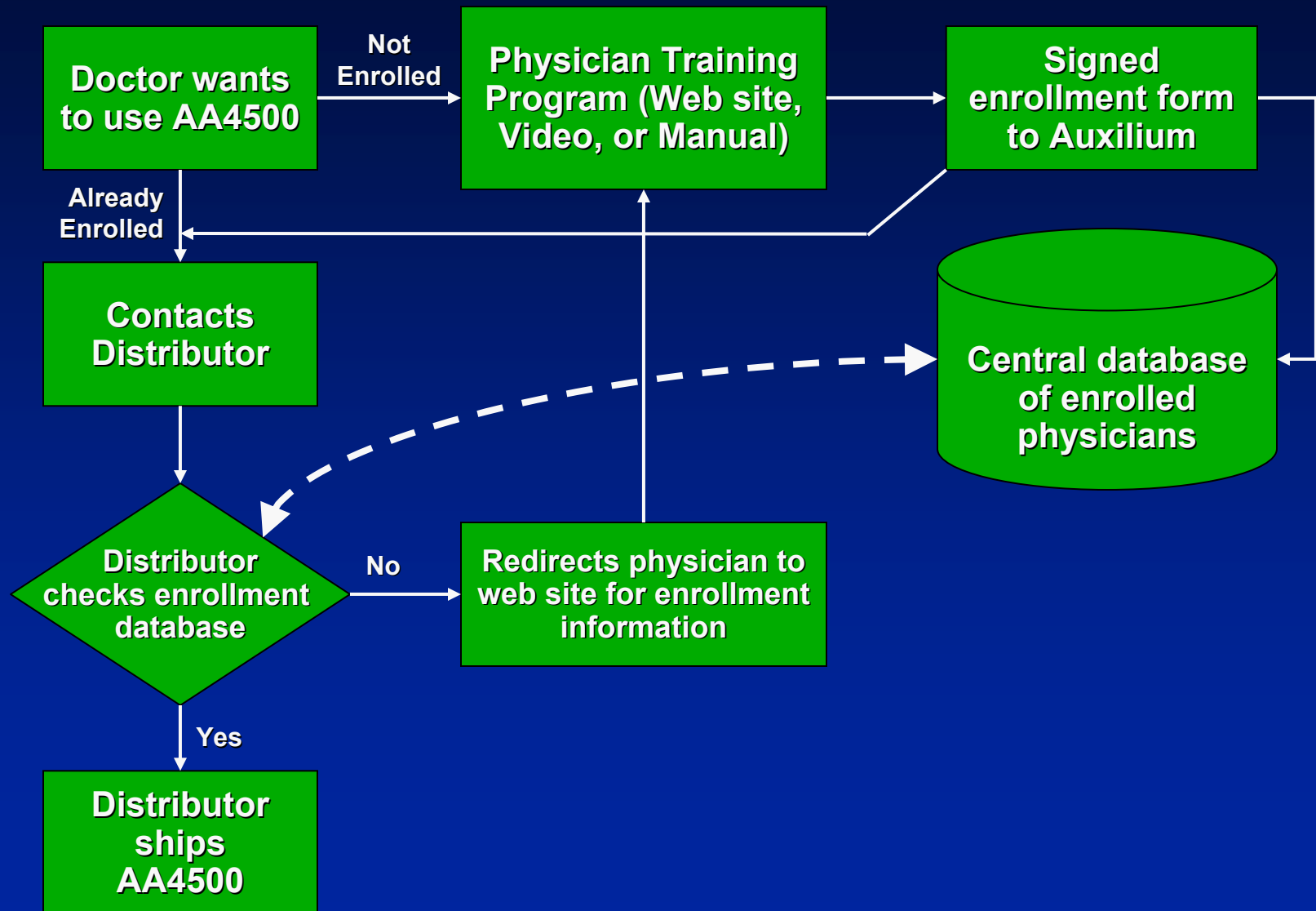
Access Management Program

Training will be required to access AA4500

Physicians experienced in the diagnosis and management of Dupuytren's Disease:

- **Must attest to completion of the Injection Training Video or manual**
- **Submit attestation to Auxilium for enrollment to receive access to AA4500**

Access Management Program



Tendon Rupture and Ligament Damage

Risk Management Activities

- Product labeling
- Physician Training Program
- Access Management Program
- **Safety monitoring**
- Patient education

Safety Monitoring

Vital To Identify Any Potential Safety Signals

- **Safety hotline to ease case reporting**
 - Training program will include information regarding case reporting
- **Aggregate safety review by Auxilium safety physician**
 - Monthly 1st year
 - Quarterly reviews years 2 to 5
- **Follow-up questionnaire in the event of tendon rupture**

Date:		
Patient Name:		
Reporter Name:		Specialty:
Address:		
City:		State:
Phone:		Fax:
Please answer the following questions related to the adverse event of tendon rupture reported for the above mentioned patient.		
1. Which finger joint (s) are affected? (Check all that apply)		
<input type="checkbox"/> PIP <input type="checkbox"/> MP		
2. Which tendon is suspected of being ruptured? (Check all that apply)		<input type="checkbox"/> Profundis <input type="checkbox"/> Superficialis
3. What was the number of injections given before tendon rupture was suspected?		# _____
4. Which joint was the cord contracting when injected? (Check all that apply)		<input type="checkbox"/> PIP <input type="checkbox"/> MP
5. What was the time since last injection to diagnosis of tendon rupture?		_____ Days
6. Was there a difficulty with the last injection, ie, suspected leakage or misapplication?		<input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, please explain:		
7. Was there any strenuous activity or excessive forces applied to the tendon, ie, work, sports, etc.?		<input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, or if there are any other extenuating circumstances, please explain:		
If yes, please explain:		
<hr/> <hr/> <hr/>		
8. Diagnostic exams used to diagnose tendon rupture:		<input type="checkbox"/> MRI <input type="checkbox"/> Other: _____
9. Results of imaging:		
10. Corrective procedures undertaken or planned:		
Training Received : <input type="checkbox"/> CD-ROM and injection manual <input type="checkbox"/> Other:		

DRAFT

Tendon Rupture and Ligament Damage

Risk Management Activities

- Product labeling
- Physician Training Program
- Access Management Program
- Safety monitoring
- **Patient education**

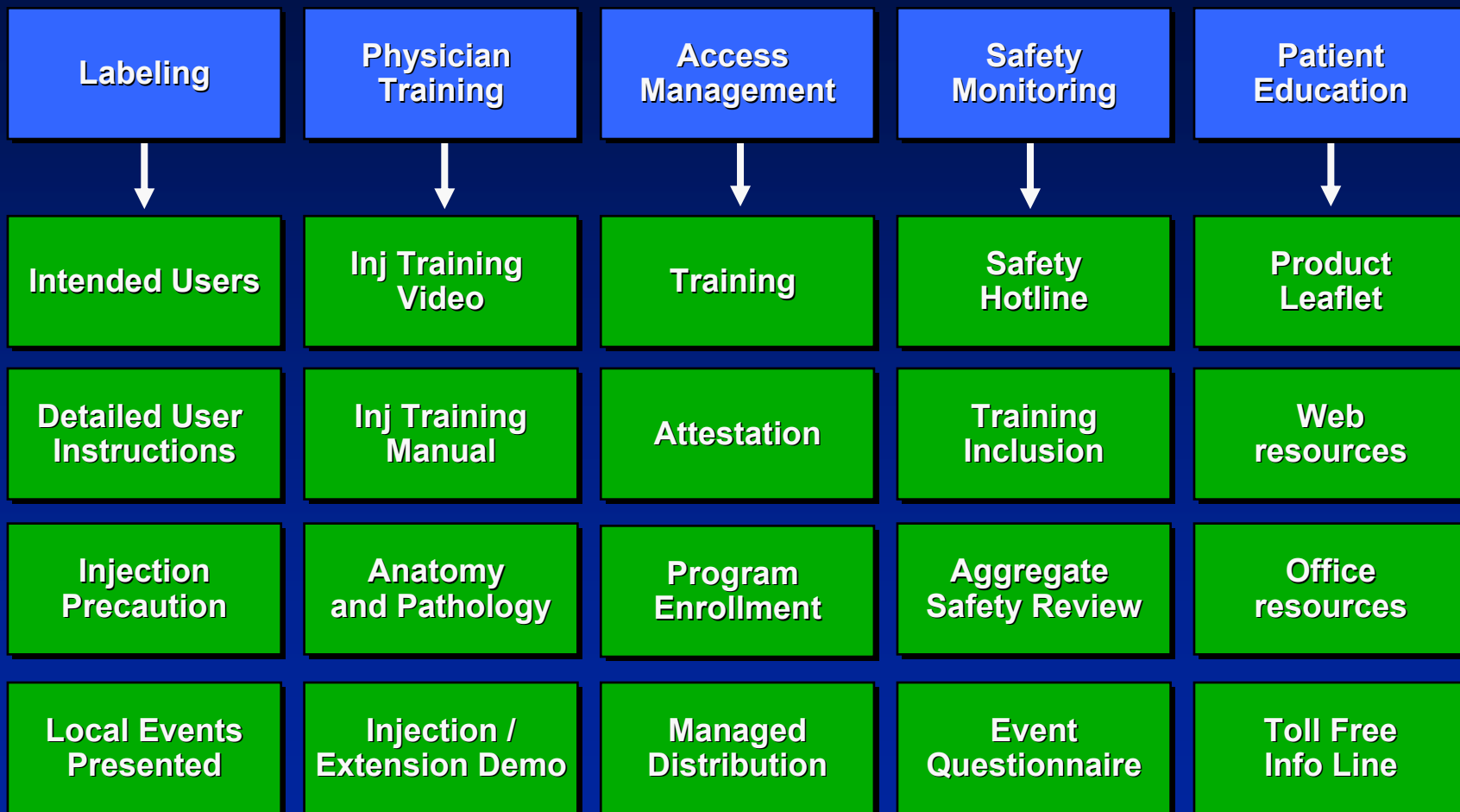
Patient Education and Support

Multiple Portals to Access Information

- **Patient Product Information (PPI)**
- **Web based resources**
 - **Disease state**
 - **Trained physician listings**
- **Office based educational materials**
- **Toll free patient product information line**

Risk Management Plan

Comprehensive to the Needs of Physician and Patient



Risk Management Plan – Goals

Ensure Appropriate Administration of AA4500

- **Recognizes potential and identified risks**
- **Creates and will implement strategies to minimize those risks**
- **Educates and informs physicians and patients**
- **Creates the optimum environment to transition AA4500 from clinical development to clinical practice**

Agenda

Introduction

Benjamin Del Tito, Ph.D.
*Senior Vice President,
Quality and Regulatory Affairs
Auxilium Pharmaceuticals, Inc.*

Dupuytren's Disease and Current Management

F. Thomas D. Kaplan, MD
*Indiana Hand Center
Clinical Associate Professor of
Orthopedic Surgery
Indiana University School of Medicine*

AA4500 Clinical Efficacy

Anthony DelConte, MD
*Chief Medical Officer
Auxilium Pharmaceuticals, Inc.*

AA4500 Clinical Safety Risk Mgmt Activities

James Tursi, MD
*Vice President, Clinical Affairs
Auxilium Pharmaceuticals, Inc.*

Overall Summary

Anthony DelConte, MD

AA4500: Summary

Anthony DelConte, MD

Dupuytren's Disease Management Today

- Dupuytren's is a debilitating condition that impacts everyday activities
- Observation and reassurance is a common form of clinical management
- Surgical therapies can straighten joints but have limitations
 - Injury to other structures (e.g., nerves and arteries)
 - Risk of infection, scarring and general wound healing issues
 - Prolonged recovery and required physical therapy
 - Re-operative risk and complexity

AA4500: Non-surgical Therapy for Dupuytren's

- **Efficacy demonstrated in three double-blind, placebo-controlled studies**
 - Each study met the 1° endpoint ($p < 0.001$)
- **Safety profile – well tolerated with broad exposure in 1082 patients**
 - AEs - mostly local, self-limiting, confined to the treated extremity
- **Enhanced physician training as part of a comprehensive risk management plan**
- **Provides the first non-surgical therapy for managing Dupuytren's Disease**